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EXPERIMENTAL STUDY OF A PATHOGENIC ACID-FAST ACTINOMYCETE (NOCARDIA) *

D. J. DAVIS, M.D., AND ONFRE GARCIA, M.D.
CHICAGO

Bollinger (1877) and Nocard (1888) discovered the organisms *Actinomyces* and *Streptothrix* or *Nocardia,* respectively, in animals. Later, Wolff and Israel (1891) and Eppinger (1890) found similar organisms in human beings. Thereafter, from time to time, many publications have appeared giving data useful for the identification of organisms of this type. The literature is very extensive.

Sometime ago, an organism of this general character was isolated from a patient at St. Luke's Hospital, Chicago. Baugher,[1] at that time, recorded the history and gave a brief description of the organism. The strain was put aside for the purpose of making a more complete experimental study at a later time.

SOURCE OF THE ORGANISM

This organism was isolated from a woman, aged about 55, who complained of subcutaneous abscesses localized chiefly on the extremities, which she attributed to wounds made by the prick of rose thorns and cactus plants, with which she had worked. The abscesses were distributed on the left foot and little toe, the right external malleous and outer side of the right thigh, the left upper arm, the right forearm and two ulcerated areas above the left breast. The lesions all presented practically the same characteristics. Some underwent resolution without ulcerating. The abscesses were red and fluctuating and contained a thick mucoid pus. The other organs were apparently normal. The patient improved after one week's stay in the hospital, and later her recovery was reported. Boric acid dressings locally and potassium iodid internally were prescribed while she was in the hospital.

The aspirated pus from the unopened abscesses in this case was examined carefully, and no sulphur granules or raylike masses were found grossly or microscopically. Filamentous branching organisms

* From the Department of Pathology and Bacteriology, University of Illinois, College of Medicine.

1. Baugher, A. H.: Tr. Chicago Path. Soc. **10**:78, 1918.

were present in smears in large numbers and were apparently pure. From the discharging abscesses also, branching forms, together with cocci, appeared. Cultures usually pure were readily obtained on several different mediums.

CULTURAL STUDIES

In general, a fairly good growth of the organism was observed, after a few days, in all culture mediums used. It is definitely an aerobic organism. In liquid mediums, there appears a striking and abundant surface growth. In solid mediums, the growth is profuse and adheres tenaciously to the surface. All give a strong earthy odor.

Plain, Dextrose and Glycerol Broth.—The transplantation of small colonies into these liquid mediums yields small conical whitish colonies, which float on the surface. About five to seven days later, the colonies unite, forming an irregular film, which extends to the wall of the test-tube. The fluid remains clear. The surface growth in the plain broth is thinner than in dextrose or glycerol broth. The latter is not only more abundant but also is a more intense pinkish orange. Particles may go to the bottom of the tube on jarring and there yield a slow growth consisting of very fine, delicate, whitish flakes.

Carbohydrate Broth (Lactose, Dextrose, Saccharose, Mannite, Salicin and Inulin).—The growth is fairly abundant in all. After four days, the mediums become more and more alkaline. The change of alkalinity starts from above and proceeds downward. No fermentation was observed in any of these sugars after one month.

Litmus Glycerol Broth.—In this medium, the growth is unusually profuse as compared with other fluid mediums. The litmus is reduced about the fourth day after the inoculation. The fluid either becomes clear and practically free of the litmus color, or it may be a slight reddish purple. The growth is intensely pinkish orange.

Litmus Milk.—The medium becomes more and more alkaline from about the fifth day; the reduction of the litmus and the digestion of the milk begin at the top. The peptonization is slow, and the milk becomes transparent and purplish blue after several weeks.

Gelatine.—Growth along the puncture line is slight and ceases after about a week, except on the surface. Liquefaction starts when the growth is quite abundant, but it is slow. The proteolytic power of the organism is evidently limited.

Corn-Starch Nutrient Broth (1 per cent.).—Apparently, the starch is utilized, but the diastatic process is slow. After one month, only two thirds of the total amount of the starch was digested.

Plain, Dextrose and Glycerol Agar.—In all, the organism grows well. The growth is notably adherent and has an irregular, warty and rugged surface. If the colonies are discrete, they have the topographic shape of a volcano, with a crater at the peak and irregular slopes.

With the aid of a magnifying glass, tiny droplets are seen on the surface of the velvety efflorescent growth. A groove is formed at the edge of the colonies, undoubtedly due to the penetration of the growth beneath the surface, thus becoming strongly adherent there.

Carrot and Potato Mediums.—The organism grows very well on both these vegetable mediums. The colonies on carrots are more intensely pinkish orange than those on potato. Discrete colonies reveal a morphology similar to that described on dextrose agar. Sometimes, the colonies are clustered with the edges turned up, forming a cuplike or honey-combed surface.

Petroff's and Löffler's Mediums.—Growth is profuse. The colonies are in heaps and are not so adherent as in ordinary agar. Liquefaction of the mediums is observed underneath and around the growth in some of the tubes.

Fresh Egg Mediums.—The surface of the shell was sterilized with alcohol and flame. The shell was then bored with a sterile, pointed scalpel and the hole covered with plaster (Johnson & Johnson). About two dozen eggs were used and incubated for different periods of time. Twenty days later, some of the eggs were opened, an abundant growth appeared (Fig. 1, *B* and *G*), and after one month's incubation, many of the eggs showed raylike forms (Fig. 1, G) and some had conidia-like bodies. The details of this growth will be given under morphology.

Sabouraud's Medium.—The growth on slants was profuse; the stab-culture showed little growth except on the surface.

Blood Agar and Tissue Cultures.—The growth on these mediums was not so profuse as on carbohydrates. No hemolysis was observed on blood agar. The tissue-culture mediums consisted of rabbit and guinea-pig liver and kidney immersed in a small quantity of broth. Growth was fairly abundant in all, and after several weeks on some of the tissues appeared a whitish surface, which, on microscopic examination, showed the formation at the tips of isolated spherical bodies (Fig. 1, *D*).

GROWTH TEMPERATURE

The organism grows equally well in an incubator (37.5 C.) and at room temperature. When transplantation is made from old cultures, development is slower than when frequent subcultures are made. Some cultures in sugar mediums were kept in an icebox at a temperature ranging from 4 to 8 C., for five months. During that time, the organism scarcely grew at all and, on the transfer of such growth to new mediums, the organism grew in only a few tubes.

RESISTANCE TO HEAT

In testing heat resistance, a culture 15 days old was selected. It was found that a temperature of 50 C. for thirty minutes never kills

and, even after a five-day exposure, growth may result on transfer. A temperature of 65 C. for ten minutes will usually kill, and for thirty minutes, uniformly so.

OXYGEN RELATIONS

In its oxygen relations, this organism is definitely aerobic; in this respect being in sharp contrast to strains of *Actinomyces hominis* and *bovis*.

MORPHOLOGY

Various morphologic structures seen in the different culture mediums are illustrated in Figure 1, *A* to *G*. Young colonies are invariably made up of tangled masses of branching filaments, the latter often with a slightly increased diameter of the main trunk. This does not always appear. Liquid cultures, such as plain or sugar broth, fresh eggs, milk, and tissue culture mediums, may give rise to quite definite structures more or less characteristic for this type of organism. Filaments 1 month old, or thereabouts, may show either large and swollen filaments or clublike enlargements, distributed here and there along the trunks (Fig. 1, *B*, *C*, *D*, *E* and *G*). They may be arranged in rosette form (Fig. 1, *F*) later becoming segmented, and freed as floating round or elongated bodies similar to spores. A definite conidia-like body may at times be found attached to the filament by means of a very fine pedicle (Fig. 1, *C*). This was observed both in fresh and in stained preparations. The filaments show no septums. The free round bodies are somewhat greenish with a transmitted light, but with no apparent double contour; as seen, for example, in *Blastomycetes*.

STAINING REACTIONS

The organism is weakly nitric acid-alcohol-fast and gram-positive in direct smears from the pus (Baugher). The young growths fail to retain the carbolfuchsin when treated with 3 per cent. acid-alcohol; but the older cultures become acid-fast. This was observed in all the culture mediums used in this study. It is also true that the degree of acid-fastness was in direct proportion to the age of the culture. Also in special mediums, such as glycerol, sugar, egg and Petroff's, the acid-fastness became more pronounced. The old filaments and the segmented forms retained acid-fastness even when 15 per cent. nitric acid-alcohol was used. These observations are in accord generally with data obtained by others in the study of organisms of this general type (*Nocardia*).

The resistance of this organism to antiformin was tested, since in cases simulating tuberculosis this method is often used. Tubercle bacilli were used as a control. Antiformin readily disintegrates all the organisms and all parts of the organism whether acid-fast or not, so

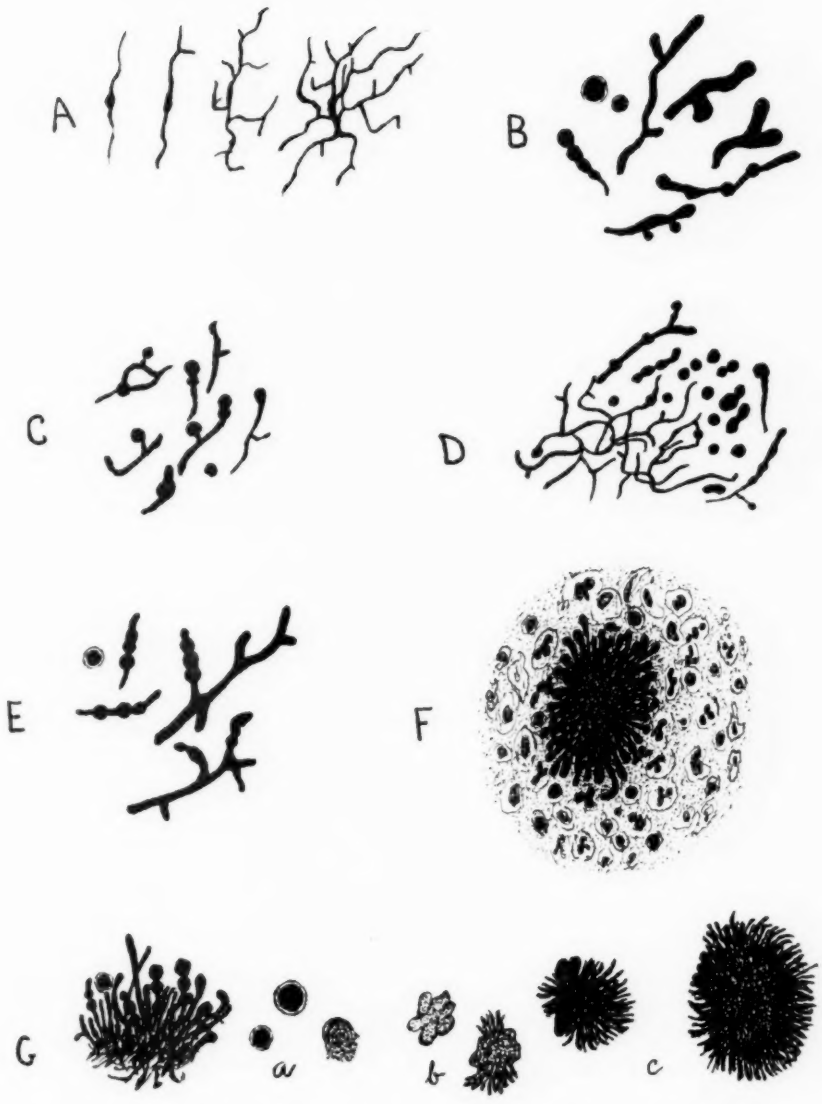

Fig. 1.—*A*, stages in the growth of the mycelium; the main trunk is somewhat larger than the branches. *B*, varieties of forms revealing swollen filaments; the spherical forms exhibit a double contour; from eggs. *C*, forms found in a broth culture 1 month old; spore bodies with delicate pedicles numerous. *D*, swollen filaments and conidia-like forms; from tissue-culture (kidney and liver). *E*, varieties of forms from a guinea-pig abscess; the material was scraped from the wall. *F*, ray-fungus obtained from an abscess in a rabbit's ear thirteen days after inoculation; the polymorphonuclear cells are relatively fewer than the mononuclear cells. *G*, several forms of the organism found in an egg one month after inoculation; these bodies occurred in the tangled masses of mycelia; a method of ray-fungus proliferation is here suggested.

that, in dealing with infections suspected of belonging to this group, this method should not be used. The nonresistance of this organism corresponds in this respect to the nocardial organism from a pulmonary case, described by one of us.[2]

EXTRACTION OF THE FATTY SUBSTANCES

Previous to the work of Bulloch and MacLeod,[3] extraction of the lipoid substances from tubercle bacilli was made by various observers, who claimed that the acid-fast property was due to these substances. Bulloch and MacLeod obtained, on cooling, a white acid-fast precipitate from a filtered extract of tubercle bacilli. The filtrate yielded also lipochromes. Further analysis of this material showed that the acid-and-alcohol-fastness of the tubercle bacilli was due to the presence of an alcohol. More recently, Benians[4] made a study of the acid-fastness and gram-positiveness of the tubercle bacillus, and came to the conclusion that the uncrushed organism is gram-positive and acid-fast, but the crushed organism is no longer acid-fast, and becomes gram-negative.

That the acid-fastness of the tubercle bacillus can be modified to a certain extent, the work of Suyenaga[5] has demonstrated. This he did by growing the bacilli on a synthetic medium, not containing substances or groups on which the acid-fastness depends, such as glycerin. He stated, however, that the acid-fastness of his strain was not thereby destroyed absolutely and that it could be recovered after repeated transplantation of the organisms in suitable mediums.

The acid-fastness of tubercle bacilli and also of the branching bacilli of the *Nocardia* type is more clearly manifested in the older growth. This has lead Soronson and other writers on the tubercle bacillus to believe that the acid-fastness of these organisms must undoubtedly be derived from metabolic products appearing in the culture mediums. This phenomenon is more evident in the case of organisms weakly alcohol or acid proof, such as *Nocardia,* as compared with tubercle bacilli.

Technic.—An acid-fast substance from the strain here under discussion was obtained and studied. Tubercle bacilli were used as a control. The method of extraction was as follows: From two flask cultures in 3 per cent. glycerol nutrient broth, 3 weeks old, the growth was transferred to an empty flask and washed with alcohol of different strengths, up to 95 per cent. (150 c.c. were used). The alcohol was

2. Davis, D. J.: An Acid-Fast Streptothrix (Nocardia), Arch. Int. Med. **14**:1-7, 1914.

3. Bulloch, W., and MacLeod, J. J. R.: J. Hygiene **4**:1-9, 1904.

4. Benians, T. H. C.: J. Path. & Bacteriol. **17**:199-211, 1912.

5. Suyenaga: Am. Rev. Tuberculosis **3**:473-475, 1919.

heated to 80 C. for three hours and filtered while hot. On cooling, a grayish white flaky precipitate was obtained, which was complete after standing from twenty to forty hours. The precipitate was acid-fast. The alcohol was decanted and the precipitate was treated with cold ether, in which it dissolved. After repeated treatment with ether and after evaporation, the precipitate became homogenous, having the appearance of a fatty substance with a decidedly reddish orange color. Extraction of the organism was completed with ether, the extracted bacteria becoming practically white. The latter when stained are gram-negative and practically non-acid-fast. The tubercle bacilli control was still strongly gram-positive and acid-fast.

In one experiment, the extracted culture was stained and presented a granular margin which was gram-positive. The spaces between the granules and the longitudinal central space took the carbolfuchsin as counter stain. The organisms were probably only partially extracted. The phenomenon could not be attributed to the stains, since the same solutions were used in several repeated instances. The fatty substance extracted was acid-fast and clearly gram-positive.

ANIMAL EXPERIMENTS

This organism is pathogenic for rabbits, guinea-pigs, rats and mice. Irrespective of the kind of animal inoculated, the lesions were practically all alike after intraperitoneal and subcutaneous injections. Intravenous injections were carried out in the case of rabbits. Practically all animals became emaciated; if they lived, they later recovered their normal weight.

Method of Inoculation.—Three tubes of broth cultures (5 c.c. each) 2 weeks old, suspended in 10 c.c. of saline solution were prepared. The disintegration of the growth by means of a glass rod in sterile test tubes yielded results different from those obtained by grinding the growth in a mortar. It was observed that the former method seemed to favor the localization of the lesions containing raylike organisms in the lung tissue, where the clustered organisms are impeded by the small capillaries; whereas, the latter method yielded no lesions containing ray forms, but only miliary nodules in the lungs as well as in other organs of the body. The amount injected was varied according to the size of the animals. The intravenous injection used was from 0.5 to 1 c.c., and the intraperitoneal injection from 1 to 2 c.c. Large doses were almost always fatal to guinea-pigs and mice. Apparently, rats and rabbits are somewhat more resistant.

All the experimental animals having shown lesions of practically the same character, a brief general description of their gross and microscopic appearance will be given here.

Intraperitoneal Injection.—From two to four weeks is about the shortest period in which lesions characteristic of this particular organism can be produced in an animal. The necropsies revealed different sizes of tubercle-like nodules scattered over the surface of the liver, the lower surface of the diaphragm, sometimes in the abdominal wall and on the surface of the intestine and bladder. The omentum contracts in folds, forming a large firm fibrous cluster of nodules. These nodules are whitish gray. The most striking features observed in the majority of the animals consist in the formation of adhesive tuberculous nodules on the surface of the liver and the lower face of the diaphragm, and in the intense inflammatory reaction of the omentum. Sometimes, there are firm strands of connective tissue, binding one part of the large or small intestine to the bladder or to a portion of an abdominal organ, such as the pancreas; and, in one instance, the spleen of a guinea-pig was somewhat enlarged, having an irregular surface covered with a yellowish gray coating. Little or no ascites fluid was found in the animals. Sections of the folded omentum showed many regions partly softened or caseous and surrounded by connective tissue. The lymphatic organs were affected, but to a limited extent only.

The microscopic change depends on the age of the nodules. The more recent lesions reveal an acute cellular reaction. Around the organism, there are many mononuclear and epithelioid cells, and next to these proliferative granular connective tissue. A few polymorphonuclears are seen. Later, the latter cells appear in larger numbers around the organisms, and the connective tissue reaction is more pronounced. Sections were made from the folded omentum, revealing far advanced lesions. Detritus of tissue and polymorphonuclear cells appeared surrounded by thick walls of connective tissue. Sections made from the different tissues showed a raylike fungus in many nodules (Fig. 2). In some, only a coil of mycelium was found. Cultures were obtained readily from the lesions.

Subcutaneous Injection.—Abscesses caused by subcutaneous injections vary somewhat with the animal used. Thus, in guinea-pigs, the abscess breaks down rather rapidly, whereas, in rabbits and rats, it tends to become more nearly chronic, and later may subside and heal. The pus is yellowish gray, and of a tenacious consistency. Evacuation of the abscess hastens the healing. Definite raylike bodies may be found in the abscesses in the rabbit's ears, which under microscope appear as tiny sulphur granules, comparable to true *Actinomyces* (Fig. 1, *F*). Scrapings from an abscess wall in the guinea-pig revealed some conidia-like formations and spherical or fusiform swellings of some of the filaments (Fig. 1, *E*). Abscesses reveal these formations in about ten

days or less. Subcutaneous injections result usually in localized infections. No appreciable lymphadenitis was observed in the groins of the guinea-pigs.

Intravenous Injection.—Injections were made into five rabbits. One showed two grayish white nodules in the medullary portion of the kidney. This was an animal injected with the organisms triturated in a mortar. It was observed that, in the rabbits inoculated with organisms prepared by the glass-rod method mentioned in the foregoing, only the lungs were affected. Furthermore, the miliary tubercles in the lungs were more abundant when this method was used than when the mortar was used, and presented many of the characteristics of true tuberculosis. The tubercles were somewhat harder in consistency and were whitish gray. Fifteen days, at least, is required for their production. Patchy fibrinous pleuritis was encountered in two animals. The injection of the organism into the lung tissue causes rapid necrosis.

The presence of ray forms in the abscesses in rabbits' ears suggested their occurrence also in sections of the tubercles of the lung and intraperitoneal lesions. Mallory's special stain for *Actinomyces* was used for their detection here. In the sections, true ray forms were found having characteristics of true *Actinomyces bovis*. In hematoxylin and eosin sections, the clubs were pink and the centers contained a purplish blue mycelium. The tubercles exhibited the structure of true tuberculosis, revealing giant cells, epitheloid cells, small and large mononuclears and granulation tissue at the periphery (Fig. 2). Plasma cells were uncommon. In certain lesions, the tubercles were invaded soon by polymorphonuclear cells which were interspersed between the clubs and the other cells. Tubercles 8 days old may show organisms which take the acid-fast stain.

Judging from the microscopic appearance of various tubercles at different stages, their formation and characteristic structure may be explained in the following way: The cluster of the organisms is retained in the capillaries. Growth then occurs, and at the same time the endothelial cells react and enlarge and become separated from the subendothelial tissue. In the meantime, the mononuclear cells are attracted by the fungus and the regional connective tissue as well as the subendothelial tissue proliferates. The endothelial cells about the organisms may become fused, forming large giant cells, as shown in Figure 2.

Comparing the various manifestations of this acid-fast actinomycetic infection with those of tuberculosis, we find that it differs only slightly. The intraperitoneal injection of the bacillus of tuberculosis produces in the guinea-pig a relatively acute serous peritonitis, with involvement of the lymphatic system, which afterward becomes general. The spleen is usually enlarged, and the animal generally dies in a relatively early

stage of the infection. With our particular organism, there is a greater tendency to form more chronic fibrotic tubercles, the animal apparently resisting the infection more strongly than is the case in tuberculosis. Generally, there is not a serous peritonitis and the spleen is not usually affected, owing probably to a lesser tendency to generalize. Involvement of the lymphatic system is a very limited and slow process. The gross lung lesions are quite the same in both infections. The microscopic pictures are also very similar. The tubercles of the acid-fast *Actinomycete*

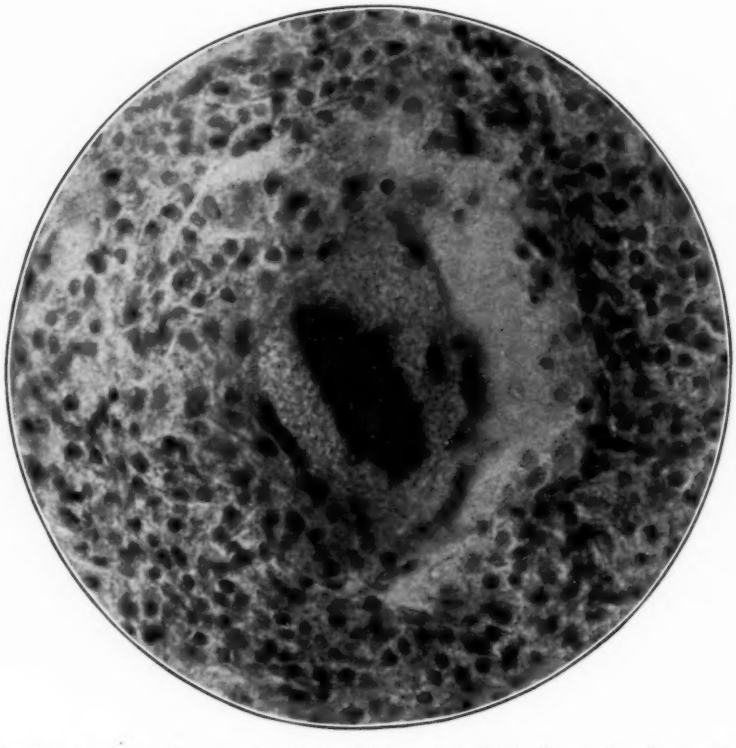

Fig. 2.—Section of experimental nodule of rabbit's lung showing acid-fast raylike fungus in giant cell with adjacent epithelioid reaction; ×600.

in the guinea-pig grow about one half as fast as those of true tuberculosis. Lesions resulting from subcutaneous injections tend to localize and, unlike tuberculosis, usually no lymphadenitis occurs.

COMMENT

As we have stated, the fresh alcohol-soluble fatty substance was able to retain carbolfuchsin and gentian violet. For this purpose, the ordinary technic for Gram's stain and for acid-fast stain was followed. Some preparations were even exposed to the decolorizing reagent and to

Fig. 3.—*A*, acid-fast stain of the organism from tissue culture several weeks old. *B*, same from litmus milk. *C*, same from broth culture. In all, sporelike bodies are seen which are not acid-fast. Swollen filaments are on the whole less resistant to decolorization. All are gram-positive.

other stains for periods of time longer than is usually necessary. It was observed that this fatty substance was more intensively colored when the stain was fixed by a low flame. Once the carbolfuchsin or the gentian violet is in the fatty substance, other stains would not replace it. Similar results were observed in staining the extracted waxy substance of tubercle bacilli, obtained through the courtesy of Dr. E. R. Long. In either case, the stain could be removed from the stained fatty substance by exposure to a warm decolorizing reagent.

Taking into consideration the work of Benians,[4] who stated that the crushed tubercle bacilli exhibited neither the gram-positive nor the acid-fast property to any appreciable extent, and also our observations as to the power of the fatty substance to retain the stain, it appears that this phenomenon is physical in character rather than chemical. In the first place, our extracted acid-fast actinomycete became gram-negative and non-acid-fast. In the second place, in the case of broken down bacilli, the liberation of the fatty substance at the moment of heating the film is greatly facilitated. Thirdly, as soon as the melting point of the waxy substance is reached, the stain is liberated when decolorizing reagents are used.

In the diagnosis of cases of either actinomycosis or streptotrichosis and nocardiosis, certain points should be kept in mind. Instances of the absence of typical sulphur granules in human actinomycosis are known and have been referred to by several authors.[6] One of us (Davis), in a case of actinomycosis of the pelvic organs, after long search in many sections and smears, found but a single ray granule, though the pus contained many branching filaments but no sulphur bodies. On the other hand, observers have noted that, while the streptothrices generally are found in the tissues as irregularly arranged branching filaments, at times they form definite bodies having a raylike structure. In this connection, too, should be mentioned the observations of Babes and Levaditi[7] who, on intrameningeal injection of typical tubercle bacilli in rabbits, found a true ray fungus arrangement with characteristic clubs, quite like those of *Actinomyces bovis*. Foulerton[8] repeated the foregoing experiments, with similar results. Abbot and Gildersleeve[9] obtained the same forms in rabbits from fifteen to thirty days after intravenous injections with Moeller's grass bacillus and Moeller's

6. Hutyra and Marek: Pathology and Therapeutics of the Diseases of Domestic Animals, Alexander Eger, Chicago **1**:677, 1916. Osler and Macrae: Modern Medicine, Philadelphia, P. Blakiston's Son & Co., **1**:1034, 1907.

7. Babes, V., and Levaditi, C.: Arch. de méd. expér. et d'anat. path. **9**:1041, 1897.

8. Foulerton, A. G. R.: Lancet **1**:551, 626, 769, 1910.

9. Abbot, A. C., and Gildersleeve, N.: Centralbl. f. Bakteriol. **31**:547-550, 1902.

timothy hay bacillus. O. Lubarsch [10] also made various experiments with different strains of acid-fast organisms and obtained characteristic ray-fungus forms with some of the strains. W. C. MacCallum [11] also obtained the same formation on injecting his strain into rabbits; and, later, Nakayama [12] made an exhaustive study of the pathologic changes, at different stages, in lesions formed by these various organisms.

Since the formation of the rays is found not only in the typical *Actinomyces bovis*, but also appears in most, if not all, representatives of the acid-fast groups, the application of the term *Actinomyces* to the entire group, as advocated by the committee on classification of the Society of American Bacteriologists, seems rational.

Conspicuous in cultures of our organism were not only swollen bulblike enlargements of the filaments, but also distinct sporelike bodies, attached here and there along the sides and at the extremities of the mycelium by delicate pedicles. Such structures are common in this group of organisms, having been noted by Foulerton,[8] Norris and Larkin [13] and others, including ourselves.[2] So far as we are able to determine, it does not appear that these structures, that is, the conidia-like pediculated bodies (Fig. 1, *C*), have been seen in true *Actinomyces bovis* or *hominis* or in the simpler *Trichomycetes*. We attempted with known strains of the latter organisms, by growing them in broth, milk, tissue and egg mediums for varying periods of time, to reproduce these bodies, which were so conspicuous in cultures of our organism in such mediums. Though irregular swellings and bulbous enlargements appeared, the definite lateral spores did not develop. We call attention to this point because of the possible differential value that it may have in the classification of this group. Such sporelike structures are common in higher forms; for example, sporothrix, but they apparently do not occur in the bacteria or in the lower types of fungi. It appears that it is in these nocardial forms that these structures first evolve.

We are not able definitely to identify this organism with any other strain of actinomycete that has been described heretofore. It corresponds closely to Eppinger's type so far as acid-fastness and pathogenicity are concerned, but it differs from it in the characteristic earthy odor of the growth and in other cultural properties. Its definite aerobic property, as well as its many morphologic peculiarities, removes it from the ordinary strains of *Actinomyces bovis* and *hominis*. Without doubt, it may be placed in Foulerton's group "A" or "I"; but further than this we cannot go. Surveying this group as a whole, we are forced to

10. Lubarsch, O.: Ztschr. f. Hyg. u. Infectionskrankh. **31**:187, 1899.

11. MacCallum, W. G.: Centralbl. f. Bakteriol. **31**:528, 1901.

12. Nakayama, H.: Arch. f. Hyg. u. Infectionskrankh. **57-58**:208, 1906.

13. Norris, C., and Larkin, J. H.: J. Exper. M. **5**:155, 1900.

the conclusion that here is a type of organism highly plastic which, on account of its lack of aggressiveness, rarely is transferred directly from individual to individual. Under such conditions, so different from those prevailing in most bacterial infections, we may understand, perhaps, why one meets with strains so variable in their properties, making the classification of them peculiarly difficult and confusing.

SUMMARY

The actinomycete here described was isolated from a human case. It is acid-fast and pathogenic for animals. It belongs in the general group of *Nocardia*.

The extracted organism is practically gram-negative and non-acid-fast. The extracted fatty substance is acid-fast and gram-positive.

The organism is pathogenic to rabbits, rats, guinea-pigs and mice. Intravenous injection into rabbits produces typical tubercles in the lungs and other organs, containing characteristic raylike bodies.

The organism may show striking conidia-like forms in liquid mediums which may be of value in identification.

The antiformin method must be avoided in a suspected case of acid-fast actinomycete (*Nocardia*).

CONTRIBUTORY FACTORS IN POSTARSPHENAMIN DERMATITIS

WITH SPECIAL REFERENCE TO THE INFLUENCE OF FOCAL AND INTERCURRENT INFECTION *

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Since the organization of the Section on Dermatology and Syphilology of the Mayo Clinic, 44,000 injections of arsphenamin have been given, and approximately thirty-eight cutaneous reactions of various types have been observed. Of this number, thirty-three were studied carefully enough, even in the earlier days of the departmental organization, to permit their use as material for the basis of certain impressions on the etiologic background and therapeutic control of these reactions.

It is not our intention merely to repeat the details of description and classification which have been so completely covered in numerous and excellent contributions to the subject by various American and foreign writers. Our concern has been mainly prevention and treatment and the study of the etiologic background in order to rationalize our therapeutic procedures. Our principal observations concern the relation of focal and intercurrent infection to the production and the course of cutaneous reactions to arsphenamin. They have led us to believe that arsphenamin is only one of several factors in many cases of postarsphenamin cutaneous reaction and dermatitis. There seems to be an induced state of hypersensitiveness, a substrate of allergic imbalance underlying the clinical manifestations resulting, in part at least, from chronic or acute protein intoxication of bacterial origin; in other words, from focal and intercurrent infections. The evidence is as yet merely clinical and circumstantial, yet rather suggestive and of some practical bearing on prevention and treatment.

Under hospital conditions which permit of close observation, the impression has grown on us that the so-called postarsphenamin dermatitis is a picture that lacks specificity. All the clinical cutaneous accidents, including the severer dermatitic reactions, can be produced

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* From the Section on Dermatology and Syphilology, Mayo Clinic.
* Read at the Forty-Fifth Annual Meeting of the American Dermatological Association, Washington, D. C., May 2-4, 1922.

by other agents than arsphenamin. The milder forms imitate a wide range of drug exanthems, toxic erythemas due to infections, the recognized exanthems, and so forth. Arsenicals in general are by no means essential to the production of typical and severe dermatitis of the exfoliative type. One of the worst cases ever seen by one of us (Stokes) was the sequel of a single injection of mercuric salicylate, and the mere painting of iodin on the skin has been responsible for other severe and extensive cases. The amount and kind of arsenical implicated varies throughout the known gamut of these compounds from sodium cacodylate to silver arsphenamin, while the picture is common to all. It seems reasonable to us, then, that exfoliative dermatitis is not solely an expression of the action of a fixed toxic agent in all cases, but involves factors expressive of the state of the recipient. We think that we have seen evidence that the susceptibility of some

TABLE 1.—Severity of Dermatitis in Relation to Number of Injections and Total Dosage

	Cases	Injections	Dosage Arsphenamin, Gm.	Total Dosage, Gm.
Severe dermatitis	9	5 to 11	2.0 to 5.6	3.24
Moderate dermatitis	12	1 to 22	0.3 to 7.4	1.85
Mild dermatitis	12	1 to 14	0.3 to 6.3	2.21

TABLE 2.—Injections Received Before Reaction Occurred

Injections	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cases	6	4	2	4	3	5	2	0	2	0	1	1	0	2

Dosage, gm.	1	2	3	4	5	6	7	8
Cases	9	6	12	0	2	2	1	1

persons is variable, and that if certain elements in their predisposing background are altered their explosive response can be accelerated, retarded, or entirely prevented. We regard the administration of arsphenamin, then, as at times merely a pull on the trigger, which discharges a load of hypersusceptibility in a variety of cutaneous explosive inflammatory phenomena ranging from urticaria through erythema multiforme to scarlatiniform erythema and exfoliative dermatitis. At other times, we suspect that the arsphenamin is the predisposing agent and that other factors are precipitating agents.

In support of these contentions, the following considerations from our experience are offered:

The dosage of arsphenamin, if the drug or its arsenic base as such is to be held responsible for the reactions, should be high in cases of dermatitis and low in those without reaction. In our experience, the contrary seems to be true. The arsphenamin dosage in cases of reac-

tion is low in the aggregate and astonishingly low in comparison with the large total doses, such as from 8 to 10 gm., which we often give in one eight weeks' course of intensive treatment. Table 1 shows that there is little evidence of correspondence between the dosage and the grade of severity of the dermatitis. From 2 to 2.7 gm. is an ordinary total for a single course of six injections in our scheme of treatment, and this single course equivalent, or less, was sufficient to bring on reaction in 70 per cent. of the patients in our series. Six of thirty-three (18 per cent.) had cutaneous reactions after the first injection of arsphenamin.

The massing of the tendency to reaction early in the course of arsphenamin treatment and with the smaller dosages is well illustrated by Table 2, in which it can be seen that the large proportion of the reactions occurs before the sixth injection, the largest single number with the first injection, and that the dosage in grams which tipped the balance is also concentrated toward the low end of the scale.

It seems difficult to imagine that a reaction attributable to an excess of arsenic as such should have a very much higher incidence in cases in which small amounts of the drug were administered than in those in which large amounts were given (Fig. 1). There seems to be an unescapable element of idiosyncrasy, hypersensitiveness or general allergic instability underlying the behavior of the patients reacting to the drug.

It has been suggested by Wechselmann,[1] and later by Eicke[2] and by Schamberg,[3] for example, that it is not the intake of arsenic but the prevention of its elimination that is responsible for the cutaneous explosions. The principal rôle in the production of this retention is played by the simultaneous administration of mercury, which by injuring the kidney is supposed to prevent the elimination of the arsenic. The following up of this hypothesis in our series, particularly in comparison with the observations of Moore and Keidel,[4] led us to different conclusions. Moore and Keidel, who have given arsphenamin without the simultaneous use of mercury, had an incidence of twenty-one cutaneous accidents in their series of 47,000 injections; eleven of them were severe, with three deaths. We, administering mercury simul-

1. Wechselmann, W.: Ueber die Pathogenese der Salvarsantodesfälle, Vienna, Urban and Schwarzenberg, 1913, 88 pp.

2. Eicke, H.: Ueber Nierensperre im Verlauf der kombinierten Quecksilber-Salvarsanbehandlung, Deutsch. med. Wchnschr. **47**:412-413 (April 14) 1921.

3. Schamberg, J. F.: Clinical Commentary on Studies of Histologic Changes in Organs Induced by Arsphenamin, by Neo-Arsphenamin and by Mercury, Arch. Dermat. & Syph. **3**:571-578 (April) 1921.

4. Moore, J. E., and Keidel, A.: Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis, Arch. Int. Med. **27**:716-747 (June) 1921.

taneously in most of our cases and using large dosages of soluble and insoluble salts and inunctions, developed, in 43,000 injections, thirty-eight cutaneous reactions, of which only ten were severe and two fatal. In other words, using large doses of arsphenamin and short intervals, especially of late, and with the systematic intensive simultaneous use of mercury, we have no higher incidence of serious cutaneous reactions than have observers who do not use mercury simultaneously. Our

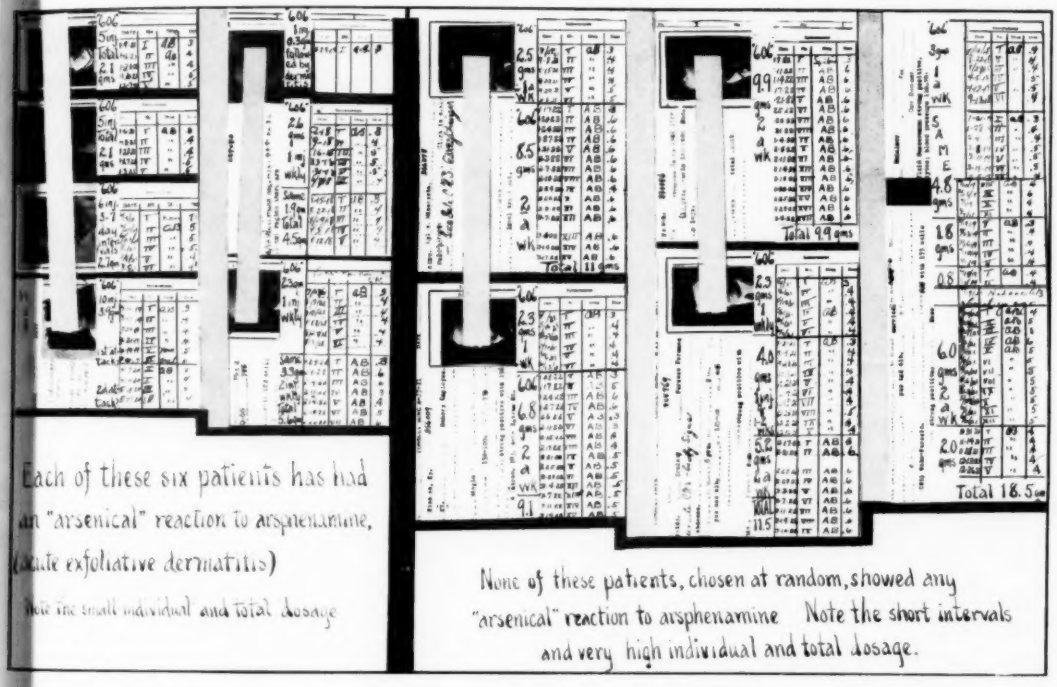
Each of these six patients has had an "arsenical" reaction to arsphenamine, (exfoliative dermatitis)
Note the small individual and total dosage
None of these patients, chosen at random, showed any "arsenical" reaction to arsphenamine. Note the short intervals and very high individual and total dosage.
Total 99 gms
Total 18.5 gm

Fig. 1. — Chart hastily constructed for a necropsy demonstration from clinical records, taken at random, of six patients who had had exfoliative reaction, including two severe and one fatal; and six patients who had had really intensive treatment. All the intensively treated patients were receiving coincidently with arsphenamin, from four to six weekly injections of mercury succinimid, usually 0.25 grains (0.01 gm.) each. Most of them received coincidently sodium iodid intravenously, from 2 to 20 grains (0.13 to 1.3 gm.) daily. None of the intensively treated patients reacted. Two of the six who reacted had received practically no mercury.

slightly higher incidence for total reactions is probably the result of the fact that we treat all patients in hospital; while Moore and Keidel treat their patients in an outpatient clinic, where minor reactions may at times escape attention. It is difficult to believe, then, on this evidence that the simultaneous administration of mercury and arsphenamin, with arsenic retention, is responsible for the development of "arsenical" cutaneous accidents.

In further opposition to the conception advanced by Schamberg and others as to the rôle of mercury in arsphenamin accidents, we find that seven of our thirty-three patients had had absolutely no mercury, and eight others had had only insignificant amounts, such as one or two succinimid injections or two or three inunctions, or a week of small doses of mercury by mouth. In all, then, nearly half of our patients who developed cutaneous accidents had had either no mercury at all, or so little that it had had no physiologic, to say nothing of pathologic, effect, and could hardly have been instrumental in producing an arsenic retention of a sufficient grade to cause a cutaneous explosion. On a service systematically using the combined administration of the two drugs, two very severe cases occurred in which less than half a dozen inunctions had been given just before the reaction.

Sept. 1, 1921, the Section on Dermatology and Syphilology increased its dosage of mercuric succinimid from one sixth to one quarter of a grain daily, and the length of the succinimid course from twenty injections to thirty. If this increase in intensity of mercurial treatment

TABLE 3.—AMOUNTS OF MERCURY RECEIVED AND GRADES OF REACTION

Patients who had never had mercury		5
Mild reactions	3	
Moderate reactions	2	
Patients who had had only trivial amounts of mercury (by mouth, six inunctions, six injections mercuric succinimid, and so forth)		6
Mild reactions	2	
Moderate reactions	4	
Patients who had had moderate amounts of mercury (from ten to twenty succinimid injections)		5
Mild reactions	2	
Moderate reactions	3	

causes a retention of arsenic in our patients, there should be an outbreak of exfoliative reactions on the service following the adoption of the new dosage system. There was, moreover, a marked increase in the number of patients placed on mercuric succinimid, because of our experience with the external irritative effect of inunctions in patients predisposed to dermatitis. While sixteen cases of cutaneous reaction developed within this period, it is significant that many of the patients had had little or no mercury. Even the fact that five who received moderate amounts of mercury had severe reactions is discounted by the fact that four other patients who had severe cutaneous reactions had had only trivial amounts of mercury, as shown in Table 3.

We could find no evidence that the kidneys of patients who had cutaneous reactions had sustained injury before, or that there was much evidence of injury during the attack. Six patients in the series had slightly abnormal urine before the attack; four of these had severe cutaneous reactions. Three of the four reacting patients had had only trivial amounts of mercury, and one had had twenty inunctions. Cer-

tainly, mercury in combination with arsphenamin could hardly have precipitated a dermatitis by causing an arsenic retention from renal injury when given in such trivial doses in the most severe cases. It is, of course, conceivable, as Eicke suggests, that injury to the kidney is not detectable in cases of combined treatment by the ordinary tests. The point we wish to make is that, in our worst cases of dermatitis, the patients not only did not show marked renal irritation before the attack or during it, *but did not have any real combined treatment.*

To the evidence [5] that syphilis itself cannot be a necessary factor in the production of cutaneous reactions to arsphenamin, we can add two cases, both of severe cutaneous reactions in which syphilis was known to be absent; one of lamblia infection and the other of tuberculous glands. Moore and Keidel also cite two cases. There was no evidence from the grouping of the cases under various types of syphilis that the disease per se had any influence on incidence. The proportions ran very much as they do in the general work of the section, each type having approximately its fair proportion for the numbers dealt with.

Our data are not well suited to a demonstration of the relative importance of neo-arsphenamin and arsphenamin in the production of cutaneous reaction.[6] It may be noted, however, that on a service in which neo-arsphenamin is used only once in nine times as compared with arsphenamin, neo-arsphenamin was being given once in six times when reaction occurred. As we are inclined to turn to neo-arsphenamin when a patient shows signs of reactivity, we believe this comparison to be untrustworthy and that, in our experience, there is at best little difference on this point between the two drugs.

Our observations suggest then, thus far, that the cutaneous reactions to arsphenamin which have occurred in our experience are not a result of the administration of arsenic and of arsenical intoxication per se. They occur early and on small total dosages under circumstances which point, not to a failure of elimination, or to overwhelming poisoning by large doses or heavy accumulation, but as a rule to idiosyncrasy and allergic instability.

In not a few cases we have seen, careful analysis shows that what would ordinarily to the uncritical eye have passed for a reaction to arsphenamin is in reality only a reaction to the cutaneous irritation of the mercurial inunction. This group of cases in which, on proper anal-

5. This is the Herxheimer theory of Pinkus, which the author evidently intended to apply largely to early exanthems.

6. On this point, Moore and Keidel cite evidence, the former from his experience with the American Expeditionary Forces, that neo-arsphenamin causes fewer cutaneous reactions than arsphenamin. This observation if substantiated may explain the lower incidence of cutaneous reaction in clinics in which neo-arsphenamin is used.

ysis, arsphenamin is found not to be the exciting cause of the dermatitis, and in which the use of the drug can be continued in full doses without ill effect, will be made the subject of a special report. The "rub dermatitis" is a definite entity in our experience, which can be controlled by certain measures, and does not, in the majority of cases, interfere at all with the continuation of the arsphenamin treatment.

Our observations further seem to indicate that the simultaneous administration of arsphenamin and mercury, even in enormous individual and total doses over long periods, does not increase the incidence of cutaneous complications in comparison with the administration of arsphenamin and mercury alternately.

We are unable finally, from our studies, to ascribe to syphilis itself or to the type of drug used, any specific or even incidental rôle in the production of cutaneous reaction to arsphenamin. The possibility that defective lots of the drug used may have a share in the complex of causes will be mentioned later.

We are forced to fall back, then, at least for a part of our explanation of the occurrence of cutaneous reaction to arsphenamin, on an allergic instability, which predisposes certain patients to reactions of this particular type. These patients, in the course of their treatment with arsphenamin, develop or possess at the outset a special intolerance of the drug, which in many cases will, under its continued use, bring them into serious complications. An important factor in the development of this state of intolerance must be our next consideration.

At this point, it may be well to insert a parenthetic but vigorous disavowal of any attempt to develop a single factor explanation to cover all cases of cutaneous reaction to the arsphenamins. Even our partial exclusion of the arsenical factor, per se, must be modified to admit that there are apparently cases, such as that of Latham, in which the arsenical intoxication is overwhelmingly important as the cause of reaction. Certain of our cases suggest that there is considerable variation in the relative influence exerted by several factors, such as the total dosage of arsenic, the element of intercurrent or focal infection and the element of local irritation.

Observations on the Element of Focal or Intercurrent Infection

Five years ago, one of us (Stokes) was impressed for the first time with the possible instrumentality of focal infection in the maintenance of a generalized dermatitis by the outcome of a case in which the patient had not secured relief. The condition of the patient, after running the gamut of all we had to offer in the way of treatment, cleared up immediately following the extraction, by another physician, of two infected teeth with granulomas at the apexes. In our next

patient, who had a generalized psoriasis, a search for foci of infection was made, and good results followed the extirpation of infected teeth. The third case thoroughly to arouse our suspicions was one included in this series, in which the immediate termination of a postarsphenamin dermatitis of ten weeks' duration followed the removal of septic tonsils. These fortuitous and, in some respects, now rather commonplace observations encouraged us to continue a search for the possible influence of intercurrent and chronic infections on the production of postarsphenamin dermatitis. While certain individual cases to be cited illustrate the point better than the aggregate, it appears from our observations of the last five years that, of the thirty-three patients with cutaneous reaction, nine had severe cutaneous reactions of the general type of exfoliative dermatitis, necessitating hospital treatment of from twenty-five to 180 days. Of these nine severe cases, seven (80 per cent.) of the patients had had serious grades of septic infection from foci or acute intercurrent infections before the appearance of the dermatitis. The emphasis on the time relation is important because many authors have noted the complications, such as pustulation in the skin and the appearance of respiratory infections, which appear to come on after the development of the dermatitis and constitute the seemingly terminal accidents in certain of the cases.[7]

In contrast to these results, we find that of the twelve patients with mild cutaneous manifestations, such as urticaria, morbilliform erythema multiforme and mild dermatitis (hospitalization less than ten days), only two (17 per cent.) carried any considerable load of infection. Even these two patients presented much less evidence of chronic infection than the severely reactive cases. The freedom of the toxic erythemas as distinguished from the exfoliative dermatitides from septic foci and from acute and chronic infections preceding the onset of cutaneous manifestations was so striking that, without knowing the identity of the individual patients in our protocols, we were able to indicate with considerable accuracy those who had had severe and those who had had mild cutaneous reactions, from the record of focal and general infection.

In our series of thirty-three patients, there were six who had no demonstrable foci of infection. Their freedom from serious trouble was pronounced. Five of the six developed only the most trivial reactions, and one a mild dermatitis of the exfoliative type of nine days' duration. This patient had a preceding acute infection that may have increased the severity of his attack.

7. It is interesting to note that folliculitis and furunculosis of the arms and paronychia became so common in the nurses managing our severe cases in the continuous and colloid baths that it was necessary to secure shoulder length rubber gloves for them. Moore and Keidel, and others.

The remaining twenty-seven patients all had demonstrable foci of infection of varying grades. Of these, one had all demonstrable foci of infection removed a short time before the actual onset of the dermatitis, which ran a severe course. This seeming paradox is explainable possibly on the theory that the foci were removed so short a time before the onset of the dermatitis that not enough time had elapsed markedly to affect the allergic condition of the patient.

Partial removal of the foci of infection demonstrable in seven patients before the onset did not apparently reduce the severity of the dermatitis. In this group, three cases were severe, one was moderate and three were trivial. It is hardly to be expected that a quantitative reduction in the severity of the cutaneous reaction would follow the removal of so uncertain a quantity as an infected tooth, for example, when other foci remained to maintain the condition.

It seems reasonable to assume that if a septic focus has anything to do with the production of an exfoliative cutaneous reaction, reaction will be likely to follow disturbance or removal of the focus during the course of a dermatitis. This is precisely what occurred in most of our patients in whom such measures were attempted. In seven patients in our series, foci of infection were interfered with during the course of their dermatitis. Five sustained flare-ups of varying severity and two were unaffected. With these seven patients may be combined the two others mentioned in whom foci were stirred up by incomplete removal just before the onset of dermatitis. The following cases are examples of the results.

REPORT OF CASES

Case 1.—A woman, aged 37, following the fifth arsphenamin injection of the second course (eleventh injection serially, total dosage 4.5 gm.) developed a typical severe exfoliative dermatitis which resisted the usual therapeutic measures to an unusual degree and was persistently moist, edematous and inclined to pustulation. Examination of the nose and throat just before the onset of the dermatitis had shown septic tonsils with fluid pus, and pus in the middle meatus on both sides, with signs of sinus infection. Not appreciating the importance of such a condition at the time, we continued the administration of arsphenamin and permitted the postponement of the treatment of the nose and throat infections. When the exfoliative dermatitis developed, the findings of infection were forgotten, but they were resurrected from the records after the explosion (as week after week passed with a steady trend for the worse), in an effort to find some explanation for the patient's resistance to all therapy. Without any conception of the possible outcome, but rather on general principles, the removal of the tonsils, which were still markedly septic, was ordered. This was done on the sixty-eighth day of the dermatitis.

The transformation was remarkable. The hospital record up to the day of the operation had read "No improvement" and "Getting worse." Forty-eight hours after the operation the note reads "Skin looks much better." On the fourth day, a personal note (Stokes) reads "Very striking improvement." The twelfth day after the operation the patient was practically well. Again a

personal note reads "Never saw such a transformation." There had been a definite and well marked exacerbation of the dermatitis during the twenty-four hours following the operation, with great increase in the edema and pustulation.

This case then exhibited the flare-up and cure that seemed to suggest direct connection between the focus and the dermatitis.

This was the first case in our series in which any attention was given to the focus of infection, and we were without presuppositions as to the possibility of securing the effect we did. Our subsequent experience showed us that a favorable outcome is not a necessary result of the effort to remove foci of infection during the course of a dermatitis.

CASE 2.—A woman, aged 46, who had had a mass in the liver suspected of being gummatous, ran a mildly reactive course under treatment. Following her fifth arsphenamin injection, she was given inunctions, and following the sixth injection she developed a patchy dermatitis, typical of the beginning exfoliative reaction. Under treatment, this dermatitis was improving rapidly, when an ill fate led us to attempt to hasten matters by removing enlarged and septic tonsils. Following the induction of local anesthesia, the tonsillar capsule on the left was incised. The patient attempted to vomit, became frightened and absolutely refused to go further with the operation, so that it was necessary to return her to her room. Had the tonsils been completely removed, the outcome might have been different. A membranous tonsillitis developed. The dermatitis began to extend, accompanied by marked edema of the face and extremities, with a rapidity that in twelve hours produced a complete generalization of what had been an almost involuted process. The skin was of the dusky livid color which, we have learned, is of unfavorable prognostic significance. The membranous tonsillitis then began to subside, and coincidently the skin began to improve. A chill and a sudden rise in temperature heralded the next exacerbation of the dermatitis, and we were again so unwise as to meddle with the patient's foci of infection, this time five infected teeth, which were extracted. The dermatitis was now at its height and was entirely unaffected by the procedure. The patient, however, showed signs of profound prostration and died on the third day after the extractions and the twenty-eighth day of the dermatitis. In this brief period, she had almost recovered, her dermatitis became generalized following incomplete operation on a focus of infection, which had amounted to the traumatic induction of a membranous tonsillitis, she had almost recovered from the tonsillitis and was at least holding her own with respect to the skin, when further meddling with another focus was followed in three days by death. Necropsy was refused.

We had evidently not fully digested the lesson afforded by Case 2 when we were confronted with another angle of the condition in Case 3. We had become convinced that the removal of foci of infection, if complete and early enough, might have therapeutic and prophylactic value. We accordingly attempted in the next case to eradicate all accessible foci, wholesale, as a prophylactic measure against dermatitis.

CASE 3.—A man, aged 59, had already shown a distinctly irritable skin. Septic tonsillar tags were removed, and thereafter several infected teeth were extracted. Signs of impending dermatitis became more marked (severe itching and irritability), and a moderate exfoliative reaction developed, with gradual onset. The patient was afebrile and in good condition. Hoping to clear up

the last of the focal infection and abort the attack, we removed five teeth on the ninth day of the dermatitis. The result was immediate and disastrous. The patient's fever rose at once to 102 F., and on the next day, following a prolonged chill, to 103.8 F. The dermatitis, which had been rather mild and was progressing favorably, underwent a violent transformation into one of the most serious exfoliative reactions we have ever witnessed. Six months later, the patient was dismissed from the hospital recovered—the longest case in our records, as a result of our attempt to abort an attack by removal of foci.

It is a matter of note that respiratory symptoms in this patient's case did not develop until the chill which followed the extractions, and that they were marked throughout the febrile part of the course, subsiding with the temperature. They were, therefore, probably primary and infectious in origin, not merely a phase of the dermatitis. The cutaneous condition began to improve with the decline in temperature.

The fourth case in our series of mistakes illustrates not only the powerful influence exerted by a focus of infection on the course of a patient already showing signs of arsphenamin idiosyncrasy, but the very great risk of creating new foci of a yet more serious type which is involved in a too vigorous attack on focal infections, and which will still further predispose the patient to reaction. Such an extension of a focus, as in this case, may establish a chain of conditions leading to a death which is at most only partially due to arsenicals.

Case 4.—A man, aged 36, had had a large amount of treatment as compared with most of our patients with exfoliative reaction (ten injections elsewhere and fourteen injections, 5.6 gm. of arsphenamin, in the Mayo Clinic). He had throughout this treatment, both before and after coming to the Mayo Clinic, presented a typical example of the so-called "fixed arsenical exanthem."[8] During the earlier injections in his course, the lesion was urticarial in character and disappeared between injections, leaving a pigmented spot. Later, the plaque was present continuously and became more eczematous in character. Six injections of arsphenamin were given during this phase of the reaction, without untoward event. Four months after the second course, the patient returned for a third, and with the first injection of this course he had a sharp rise in temperature, following a chill. An erythema appeared on the arms, but presently subsided. It should be noted at this point that a cutaneous test with arsphenamin was negative, but that the test was a scarification test which, according to Stuart and Maynard,[9] is unreliable.

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8. Fuchs, D.: Fixe Salvarsanexanthem, Deutsch. med. Wchnschr. **45**:1276-1277 (Nov. 13) 1919. Schönfeld, W.: Fixe Salvarsanexantheme, Deutsch. med. Wchnschr. **46**:11-12 (Jan. 1) 1920. Leibkind, M.: Beitrag zur Kasuistik der Salvarsan exantheme (fixes exazerbierendes Erythem), Dermat. Ztschr. **31**: 91-97, 1920. Thibierge, G., and Mercier: Taches érythematopigmentées à répétition "in situ" à la suite d'injections de novarsénobenzol, Bull. Soc. franç. der dermat. et syph. **93**: 1919. Kraus, A.: Fixe Salvarsanexanthem, Deutsch. med. Wchnschr. **46**:913-914, 1920. Nägeli, O.: Fixes Neosalvarsan exanthem und Adrenalinwirkung, Cor.-Bl. f. schweiz. Aerzte **47**:1291-1298 (Sept. 29) 1917.

9. Stuart, H. C., and Maynard, E. P.: Hypersensitiveness to Arsphenamin Following Exfoliative Dermatitis; a Cutaneous Test, Arch. Int. Med. **26**:511-520 (Nov.) 1920.

As the patient had had a sharp meningeal relapse in a severe neurosyphilis, it was deemed necessary to push the treatment vigorously. In order to prepare him for it, all foci were ordered removed. An infected impacted third upper molar was the first focus attacked. The removal of this tooth proved the beginning of a series of septic accidents which, in combination with the treatment, carried the patient steadily down hill to a fatal issue. There was tremendous reaction to the extraction, but the skin remained clear while the arsphenamin was continued at the rate of two injections of 0.5 and 0.6 gm. a week. The operation had exposed part of the mucosa of the antrum, and an extension of the infectious process resulted in a severe infection of the antrum. Notwithstanding this serious increase in the extent of the septic infection, the six injections of arsphenamin were well tolerated and the antrum infection began to subside. The spinal fluid taken at the end of this series showed a most remarkable response. Had we been wise enough to discontinue all

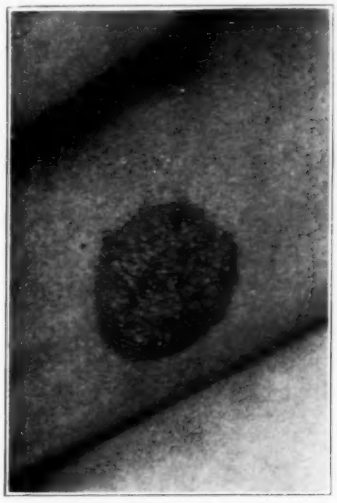

Fig. 2 (Case 4).—"Fixed" arsenical exanthem on the flexor surface of the forearm. This was the only lesion present. Originally urticarial, it recurred at first with each injection and finally became a lichenified eczematous hyperpigmented plaque.

treatment at this time, further trouble might have been avoided. But, with the sixth injection, a slight rise in temperature and a diarrhea developed. The presence of a large amount of pus in the urine was taken as an indication for a cystoscopic examination, following which there was a sharp reaction. A seventh arsphenamin injection was given. This was followed by a sharp febrile reaction and the first appearance of a true dermatitis. This slowly extended, but never at any time reached the proportion of a really severe exfoliative reaction, although, because the patient died, we have classified him with our severe cases. During this period of the patient's gradual decline, the infections of the jaw, antrum and ethmoids and the diarrhea persisted. The dermatitis, while moderately extensive over face and back, was on the whole mild. The antrum was drained, and for several days the patient showed distinct improvement. Herpes appeared on the lip. Still another extension of the infectious

process now occurred. The patient "caught cold," the throat became sore, and there was considerable coughing, and pain in the chest. A special examination by the thoracologist revealed acute coryza with mild acute bronchitis, but there were as yet no pneumonic signs. The diarrhea was persistent, and pharyngitis and stomatitis appeared. The dermatitis began to extend again with the onset of this new infection, but never at any time became general, involving chiefly the malar prominences and the back. Proctoscopic examination disclosed only a diffuse proctitis. Prostration steadily increased, and on the fifth day of the "cold" the patient had a sudden cardiac failure and died.

The terminal picture was that of bronchopneumonia with beginning empyema. The colon and rectum showed an extensive ulceration which had evidently developed in the five days since the proctoscopic examination.[10] Careful search for evidence of "arsenic death" was made, but results were disappointing. The degree of fatty change in the liver particularly was much less than was expected, and certainly no more than would be in keeping with a death from chronic septic infection rather than pure arsenical intoxication. Large amounts of arsenic were found in the liver by the microchemical method of Justus,[11] but this was to be expected as the liver is the principal storage depot for the drug. There was little or no arsenic found in the skin by this method, which would be surprising indeed if cutaneous reaction is a direct irritative effect of arsenic as such. Much arsenic was found in the wall of the intestinal tract immediately below the mucosa, a point which will be discussed presently in connection with the findings and histories of other patients with diarrhea.

Here, then, we have an excellent example of the puzzling interplay between infection and arphenamin intoxication. It is difficult indeed to say just what the rôle of either may have been. The patient had long shown evidence of a certain type of iodiosyncrasy to arsphenamin, in the form of the "fixed" cutaneous reaction, yet he seemed highly resistant to a true exfoliative dermatitis. He sustained sixteen injections of arsphenamin with good therapeutic results and only a trifling reaction, until a steadily increasing load of intercurrent infection overbalanced him and the true exfoliative reaction appeared. Yet this cutaneous reaction never reached its full development; for, before it could generalize, the infection overwhelmed him, and he died of streptococcal infection rather than of arsenical poisoning. Infection preceded cutaneous reaction throughout the latter part of the course. The necropsy finding of empyema in this case stands unfortunately as the chief witness to the streptococcal character of the preceding and the terminal infections, for the body had been embalmed before the family was finally persuaded to permit necropsy. It was fairly apparent at postmortem that the patient had died as a sequel to infection rather than of arsenical poisoning. From the study of the sequence of events in such a case as this, it seems not at all improbable that the terminal

10. This will be discussed with the intestinal findings in another case.

11. Brünauer, S. R.: Ueber mikrochemisch-histologische nachgewiesenes Arsen bei Hyperkeratosis arsenicalis, Arch. f. Dermat. u. Syph. **129**:187-198, 1921.

and intercurrent infections described in the literature in exfoliative dermatitis are not necessarily superimposed on the dermatitis, as most writers suggest. They are parts of the systemic background, developed from focal to general proportions in the course of a complication which owes its characteristics to the combined action of an infection, or of an allergic state secondary to infection, and the toxic action of arsphenamin and arsenic as such.

Summary of Effect of Interference with Focus of Infection.—It appears then from our series of observations that the focus of infection, so conspicuous in the severe cases in our series and obviously of so much less import in the mild cases, bears more than a general statistical relation to the problem. The complete removal of an important septic focus in a case of intractable dermatitis may result in rapid and almost miraculous cure, as in Case 1. Such results are not usual, however, early in the course of the dermatitis. In subsequent cases in our experience, it became evident that interference with a focus of infection, even to the extent of complete extirpation, would not necessarily abort the dermatitis, was likely to result in rapid extension and generalization of a mild and comparatively restricted lesion and might lead to a fatal termination. Our theory that a focus of infection is instrumental in the production of postarsphenamin reaction conforms, then, to certain of the criteria recognized as constituting a clinical demonstration of the etiologic relation of a focus to its pathologic sequelae. The focus, if disturbed, may cause an exacerbation of the process, and removal may in some instances cure it. On the other hand, its part in the process is indirect. It prepares the soil but does not produce the pictures as such. Accordingly, mere removal of the focus may be slow to produce effects, since the induced allergy only gradually subsides. We concede that our group of case demonstrations is small, but as it is marked by a high mortality rate, further proof of these two relations in man will be involuntary on our part. One patient in our experience, who exhibited a marked flare-up following the extraction of four teeth on the sixth day of a dermatitis, fortunately escaped serious consequences. Another, on the fourteenth day of the dermatitis (second attack), had three teeth removed, with a marked exacerbation of her dermatitis but without rise in temperaure. She also, fortunately, escaped further untoward effects.

As a practical maxim, then, we advise against removing or stirring up any focus of infection during the attack of dermatitis, unless an unusually prolonged siege and chronic changes accompanied by an easily accessible, very septic focus, completely removable at a single operation, can be demonstrated. It is especially serious to undertake removal of teeth when an extension into inaccessible tissues, or to other teeth as

yet only slightly involved, may aggravate the septic process instead of removing it, and have the most serious effect on the dermatitis.

Removal of a focus of infection can be accomplished after dermatitis has completely subsided, without ill effect. We therefore suggest, tentatively, that, if it is not possible to dispose of foci of infection routinely some time before treatment is begun in order to control cutaneous hypersensitiveness to arsphenamin, it should be postponed until a rest interval. If it is done after any form of cutaneous reaction has appeared, great care must be exercised to select cases that do not exhibit the eczematoid, patchy, true dermatitis, which is the warning or beginning of grave exfoliative reaction. In five cases, we removed foci of infection from two weeks to nineteen months after complete recovery from the attack, without untoward effect.

Acute Infectious Prodrome of Dermatitis.—The foregoing observations on the relation of a focus of infection to the cutaneous arsphenamin reactions may now be supplemented by certain further observations on the possible relation of reaction to the occurrence of prodromal acute infection, on the character of the fever, the diarrhea, the association of dermatitis with jaundice, attempts at cultural isolation of an organism and a certain degree of epidemicity or, better, of recurrence of cutaneous reactions in association with other phenomena of a suspected but not as yet demonstrably infectious origin.

Of thirty-three observed cases, data on the presence or absence of a previous infection were obtained in twenty-nine. Of these, ten give evidence of an acute infection preceding the onset of the dermatitis. The following is a résumé of these cases.

Case 5.[12]—A woman, aged 40, four days after the second arsphenamin injection (no mercury given), had developed pharyngitis, tonsillitis, palpable cervical glands, hacking cough, audible ronchi, running nose, and a temperature of 101 F. A papular dermatitis appeared on the arms. The attack was aborted by our usual technic, but later the patient had a relapse and a mild dermatitis of ten days' duration. The tonsils showed evidence of chronic infection.

Case 6.—A woman, aged 36, had pharyngitis and slight fever (99.5 F.) before the first injection, but dermatitis did not appear until after the fifth injection.

The patient in Case 1 developed sore throat and earache the day of the first injection. There was no fever. Dermatitis appeared twenty-eight days later, following the fifth injection. Examination of the nose and throat just before the eruption appeared revealed reddened tonsils from which pus could be expressed in moderate amount, and pus from both sides of the nose suggestive of antrum infection.

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12. The details of this case with discussion were published by Stokes, J. H.: Control of Exfoliative Dermatitis Following Arsphenamin Administration, Med. Clin. N. America **5**:498 (Sept.) 1921.

The patient in Case 4 developed infections of the jaw and antrum following extraction of an impacted third molar. The reaction was severe. The infection of the antrum continued and at necropsy it was shown to have extended into the ethmoids. Bilateral bronchopneumonia, with beginning empyema, was the terminal picture. The dermatitis had appeared after the eighth arsphenamin injection and twenty days after the onset of infection of the antrum.

Case 7.—A man, aged 44, had had tonsillitis of three days' duration eleven days before the dermatitis appeared. The tonsils, which were extremely septic, were removed without reaction four days after the acute attack of tonsillitis and four days before the dermatitis appeared.

Case 8.—The patient, the day following the second injection of arsphenamin, had pain over the left eighth to twelfth ribs, with râles at the left base. There was no cough, no sore throat and no evidence of embolism. The next day the dermatitis appeared.

Case 9.—A woman, aged 41, had an unexplained fever of 101.5 F., for two days before signs of the dermatitis appeared. Two weeks later, during the exfoliative attack, severe tonsillitis with exudate and a temperature of 102 F. developed.

Case 10.—A woman, aged 30, developed acute sinusitis and otitis media following extraction of an impacted molar. This lasted until two weeks before the first arsphenamin injection. At the end of a Pollitzer course of three injections, a cold in the head developed, without fever. Dermatitis appeared three weeks later, after three more injections at weekly intervals.

Case 11.—A woman, aged 32, developed diarrhea six days after one injection of 0.3 gm. of arsphenamin. Ten days later, she developed a sore throat and, on the eleventh day, a marked toxic erythema, eczematous about the ears, which involuted in four days under treatment.

The effort to associate an infectious process with a dermatitis simply on the basis of a chronologic sequence is, of course, open to the usual *post hoc propter hoc* objections, and at times leads to what seem to be far-fetched interpretations. We do not wish to be understood as rating the occurrence of an acute infection or of acute exacerbations in a chronic process as directly causative of the dermatitis. We feel rather that they assist in preparing the allergic substrate on which the various agents responsible for the relatively nonspecific manifestations of the cutaneous reactions operate to produce an anaphylactic explosion. In certain cases, particularly such as Cases 1, 4, 5, 6, 7, 9 and 10, the infection basis comes to clinical recognition at its onset, and then subsides into a chronic phase, with relapses sometimes before and sometimes during the course of the dermatitis. This indicates that complete recovery did not occur, but that flare-ups in a state of more or less chronic sepsis followed the acute attack and maintained the sensitized background for the cutaneous reactions. In Case 8, an infectious or

embolic accident immediately preceding the dermatitis may or may not have been a factor in precipitating the reaction, and may also have been the culmination of an infection harbored for some time. Case 11 brings up the question of diarrhea as a prodrome and a possible manifestation of an infectious element in the conventional picture of certain cases of cutaneous reaction to arsphenamin.

It should be noted that, of the nine patients with acute, apparently infectious incidents preceding their exfoliative reactions, seven had demonstrable foci which might have made them chronic carriers of infection, and three of these had very severe attacks of dermatitis.

Fig. 3.—Severe stomatitis in a case of relatively mild dermatitis. This stomatitis recurred twice after successive injections of arsphenamin before any dermatitis appeared.

PATHOLOGIC CONDITIONS ACCOMPANYING EXFOLIATIVE REACTIONS

Diarrhea and Exfoliative Reactions.—In fifteen of thirty-three cases, data on attacks of diarrhea preceding the onset of exfoliative reactions were obtained. Of these thirty-three patients, six had had attacks of diarrhea before treatment for syphilis was begun; only two, however, had diarrhea during the exfoliative dermatitis. There seems, then, to be no striking relation in the aggregate of so small a group between diarrhea before and during dermatitis. But it is rather

interesting and significant that in none of our earlier cases in 1917, 1918, 1919 and 1920 was there diarrhea, even though the dermatitis was severe. Diarrhea developed in each of five cases, mild and severe, which form the "1922 epidemic" in our series. All these cases appeared in the fall and winter of the present year, and in two of the five there were histories of repeated attacks of diarrhea before treatment was begun. The observations on the individual cases are more suggestive.

The patient in Case 4 came to the clinic originally for diarrhea. He had a fistula in ano with an anal ulcer, and had had ulcers in the rectum, thought possibly to be syphilitic. Seventeen days before his death, and before the onset of dermatitis, he developed diarrhea. Yet as late as five days before death, ulcers could not be found in the rectum or sigmoid, and proctoscopy showed only a mild colitis. The tremendous ulcerative involvement present at necropsy developed apparently with fulminating rapidity in the five days that marked the onset of the terminal streptococcal accident and its fatal termination. At necropsy, an old high stricture showed that the process was old, possibly associated with nonsyphilitic ulcerative colitis.

This case of colonic ulceration possibly associated with a terminal streptococcal infection should now be compared with another case observed in the same group of the past winter in which the patient developed, early in the course of her dermatitis, from which she fortunately recovered, an ulceration of the colon even more extensive than that of the patient who died. This colonic ulceration was recognized by proctoscopy on the twenty-fifth day of the dermatitis following bleeding two days before. The diarrhea, however, had appeared coincidently with a chill and rise of temperature on the eleventh day of the dermatitis, and was accompanied by a definite cutaneous flare-up. The ulceration of the colon in this patient was remarkable, not at all a simple toxic diarrhea. The ulcers were punched out, and one of them perforated the rectovaginal septum, forming a fistula within fifteen days after the appearance of blood in the stools. Cultures of the stools yielded only indifferent organisms; but Dr. Buie by proctoscopic examination obtained swabs direct from the bases of the ulcers, on the eighteenth day of the diarrhea, which on culture yielded numerous chains of streptococci and some staphylococci. Dextrose broth cultures yielded only colon bacilli. Blood cultures taken at this time were negative.

The demonstration of streptococci in more than merely accidental numbers in the colonic ulcerative lesions in this case may then be paralleled with the fulminating appearance of colonic ulceration, which seemed coincident with a terminal streptococcal infection in the case terminating fatally (Case 4). Ulcerative colitis did not develop in the other patients of this group who had diarrhea. Widal tests done on

several of this group of diarrheic patients were negative, and stools were negative for the bacillus of Flexner, Shiga's bacillus and *Bacillus typhosus*.

Our observations on the diarrhea in certain cases of exfoliative dermatitis, while inconclusive then, certainly suggest that while the predisposing cause may be arsenic at times, the exciting cause may be the streptococcus, whose activities seem to appear and reappear throughout the courses of cutaneous reactions to arsphenamin which we have observed.

It is interesting to note that we at first ascribed the diarrhea, which was so novel in our cases during the last few months, to the use of improperly prepared Fischer's solution, which we suspected might be hyperalkaline. Careful investigation showed no ground for the suspicion. The formula and preparation were evidently the same as that which we had been using for four years in the treatment of all the preceding cases of cutaneous reaction not associated with diarrhea.

Stomatitis.—This condition, as an accompaniment of exfoliative reactions to arsphenamin and other arsenicals, receives mention frequently in the literature. In our series, such association was comparatively infrequent; only six cases exhibited it. In three, the stomatitis was mild, and in three, severe. One of the severest cases of stomatitis (Fig. 3) was accompanied by a relatively mild cutaneous reaction. The other two severe cases accompanied severe dermatitis, and both patients had ulcers in the colon. The process in the mouth and throat reached an ulcerative stage in both, but cultures were not made. The remaining cases were comparatively mild and were evidenced by redness and dryness of the mucosa. It is, of course, impossible to establish any relation between a possible focus of infection and the stomatitis on any such basis; but it is worth noting that in all the cases of stomatitis there were well marked focal infections in the mouth and throat.

Fever.—Ten of the thirty-three patients had fever just before the appearance of the dermatitis. In five, the cutaneous reaction was mild, in four, moderate and in one, severe. Half of these patients with fever at onset had other definite evidence of what appeared to be an acute infectious process; one had acute antrum infection, three, bronchitis and one, rhinitis and pharyngitis. Of the five remaining patients without acute infections, four had definite foci of infection. It appears, then, that a large proportion of patients with fever before the onset of the dermatitis had infections, active or latent.

Fever occurred in the course of the dermatitis, but not at onset, in twelve patients. In five, the condition was severe, four having physical signs suggestive of intercurrent infection. Four had foci of infection and the fifth had had septic foci removed just before the outbreak. Five had moderate dermatitis, two of whom had had foci

of infection stirred up by intervention; and one had signs apparently of intercurrent acute infection. Of the two patients whose conditions were mild, one had foci of infection (septic tonsils) removed eight days before the onset of dermatitis and the other had signs of acute intercurrent infection.

It appears, then, that two thirds of our patients with cutaneous reaction had fever, half just before and half during the dermatitis, and that half of those who had fever had signs of associated intercurrent infection, and one third had foci of infection. All told, seventeen of twenty-two patients with fever had foci. This certainly makes a liberal proportion whose fever is interpretable as a manifestation of infection instead of chemical intoxication. That the fever preceded the dermatitis in half of the cases seems to speak against a disturbance

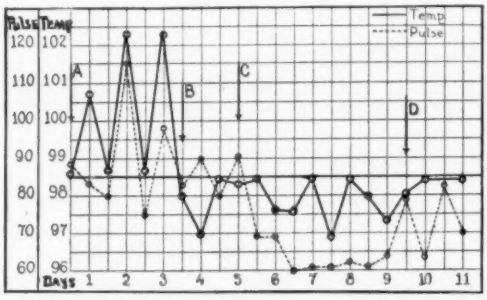

Fig. 4.—Typical mild erythematosquamous reaction to arsphenamin. *A*, arsphenamin, second injection, 0.2 gm., sharp febrile reaction; *B*, dermatitis over arms, shoulders and legs; *C*, temperature normal; *D*, dermatitis gone.

of the cutaneous part of the heat-regulating mechanism, suggested by one observer.

Eleven patients, or only one third, did not have fever before or during their dermatitis. Of these, three had severe dermatitis, four, moderate and four, mild. It is apparent from both these groups that the severity of the dermatitis is not a factor in the development of fever, or the reverse. Of those who had no fever, six had foci of infection and two others had acute infections, including acute tonsillitis just before the attack, acute infection of the antrum, and otitis media, and sore throat with earache. This last mentioned symptom, however, was not accompanied by enough signs to support the diagnosis of an acute infection.

It is again apparent that even in afebrile cases the possibility of an underlying low grade infection as a factor cannot be wholly lost sight of. The study of individual cases rather than aggregates brings

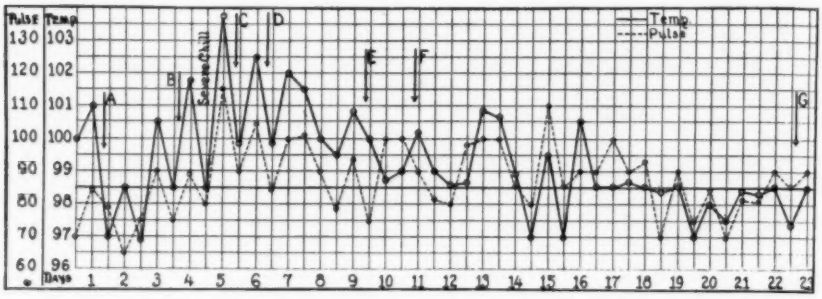

Fig. 5 (Case 3).—Effect of removal of a focus of infection in causing a flare-up of a dermatitis, followed by subsidence of temperature to normal, and gradual recovery. In this case there seems to have been an association of the chronic focal infection, the fever and the dermatitis; a fortunate outcome of a rather risky procedure. *A*, entered hospital with marked dermatitis of neck and chest, with some oozing; *B*, extraction of infected teeth, followed by chill and sharp rise in temperature; *C*, marked "flare-up" of dermatitis, which generalized at once; *D*, conditions very much worse; oozing and desquamation pronounced; *E*, much improved; temperature subsiding; *F*, more improved; *G*, "feels fine;" temperature normal, and remained so; steady improvement in cutaneous condition; dismissed from the hospital on the forty-seventh day.

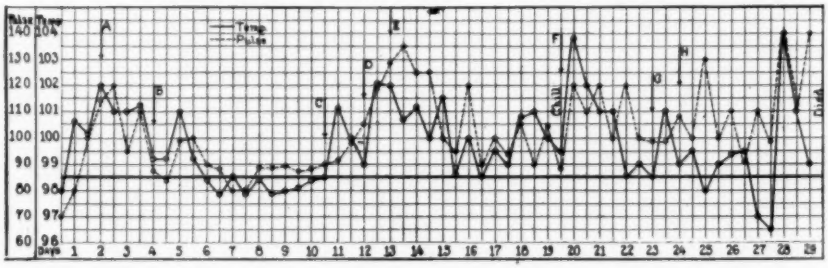

Fig. 6.—Effect of interference with foci of infection on the course of postarsphenamin dermatitis. *A*, fever accompanying extension of dermatitis after sixth arsphenamin injection; *B*, fever subsiding, dermatitis improving; *B-C*, dermatitis clearing up; *C*, skin almost clear; tonsillectomy attempted, patient refusing to permit completion of operation after tonsillar capsule was incised; febrile reaction; *D*, membranous tonsillitis developed, fever higher, eruption previously almost gone, extending rapidly; *E*, eruption completely generalized, dusky livid hue, edematous, face swollen; *E-F*, tonsillitis improving, eruption somewhat less edematous and livid; *F*, sharp chill, few râles at base of lungs, otherwise clear; skin exfoliating; *G*, five teeth extracted, moderate reaction; no change in skin; *H*, patient failing, scaling more pronounced; steady decline until death five days later.

out some of the possible relations between an acute infectious process and the dermatitis syndrome. This is accomplished by means of charts (Figs. 4, 5, 6, 7 and 8).

It is, of course, impossible to give too great weight to evidence of this sort tending to show that the fever is a manifestation of infection rather than of drug intoxication as such. Fever is an expected accompaniment of either, and of the anaphylactic reaction state as well. We merely wish to show that, in many cases, it fits into a syndrome, and it is quite as logical to interpret it as an infection, often prodromal, as to interpret it as a mere accidental complication or symptom of intoxication as such.

Pulmonary symptoms and catarrhal inflammation of the gastrointestinal tract have been recognized in the literature as part of the clinical picture of arsenical intoxications. The inclination is, of course,

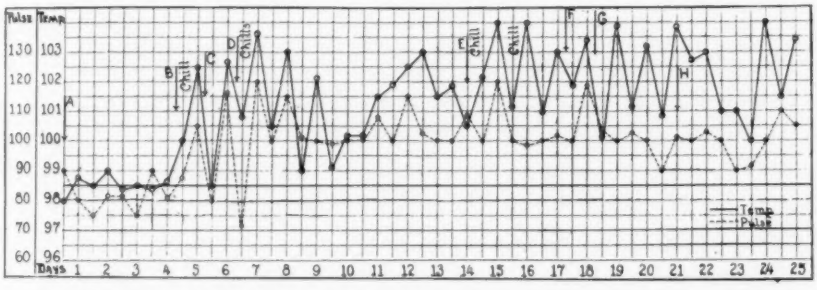

Fig. 7.—Until the winter of 1921-1922, we had never seen diarrhea with postarsphenamin dermatitis. During this winter, other patients of the Clinic, including especially those observed postoperatively, had a peculiar dysentery. Part of the outbreak was traced to the Flexner bacillus, but there was no trace of such an organism in this case. In another case of severe dermatitis occurring at about the same time, streptococci were obtained from the swabs of the rectal ulcers, but none was found in the blood or stool. *A*, afebrile onset, mild dermatitis of the arms and legs; *B*, onset of diarrhea, associated with sharp chills, abdominal cramps and rise in temperature; *C*, skin much worse, dermatitis rapidly generalizing; *D*, diarrhea beginning to subside; *E*, chill, another sharp rise in temperature, beginning to cough severely; moist râles, signs of pneumonitis, pericarditis; *F*, diffuse bronchitis, signs of pericarditis; skin better; *G*, diarrhea beginning again and skin much worse; *H*, ups and downs suggesting septic condition, with gradual recovery in ninety-one days.

to ascribe to the drug the production of manifestations in the mucous membrane as well as the cutaneous eruption. We desire to point out, however, that in conditions such as erythema multiforme, erythema scarlatinoides and the epidemic type of dermatitis exfoliativa (Savill's disease), all of which are known to be associated with infection, particularly streptococcal and staphylococcal, the clinical accounts given by various authors accord quite well with those of the various clinical

types of arsphenamin reactions, and the constitutional symptoms have much in common with them. There is, therefore, nothing intrinsically impossible about an infectious background for many of the clinical signs, besides the fever, which appear in the course of an exfoliative reaction to arsphenamin. Given the same signs in the absence of a history of arsphenamin treatment and dermatitis, we would unquestioningly accept them as evidence of intercurrent infection. It must be conceded, however, that consultants in a case such as Case 6 could not agree with regard to the interpretation of the systemic signs through the course of a long illness. Signs of diffuse pneumonitis, of pericarditis and of endocarditis were reported by certain observers and reversed by others of equal competence, so that in the end we were left with the temperature chart of a septic infection, with chills at the onset, and a general disagreement as to whether a septic infection had or had not been a factor in the symptoms.

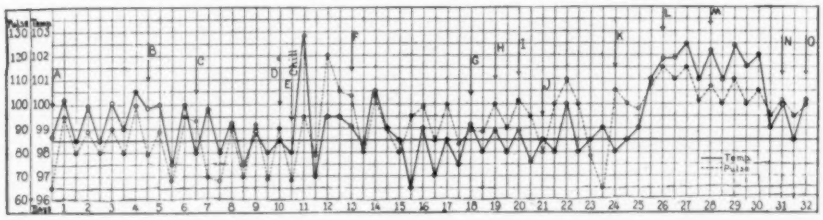

Fig. 8.—Chronic infection from interference with a focus, combined with arsphenamin accidents and fatal septic termination. *A*, slight septic temperature following exposure and infection of antrum in removing infected impacted molar twelve days before; no dermatitis; *B*, antrum involved; *C*, sixth injection of arsphenamin, 0.5 gm.; temperature subsiding, condition improved; *D*, cystoscopic examination with slight systemic reaction; urine had contained pus; *E*, seventh arsphenamin injection, 0.6 gm., chill and sharp reaction; *F*, first appearance of dermatitis, back and iliac crests; *G*, skin clearing up rapidly; no more arsphenamin given; *H*, focus in upper jaw beginning to drain again, fistula, probably antral; diarrhea began; had had rectal ulcers and diarrhea before coming to Clinic; *I*, antrum evidently worse, skin also definitely worse, extending dermatitis; *J*, antrum drained; diarrhea persisting; dermatitis stationary, not general; *K*, fresh infection; patient has "cold," sore throat, pain in chest, râles, diarrhea, severe; sharp rise in temperature; *L*, dermatitis spreading again, face involved; *M*, diffuse proctitis, no ulceration; *N*, failing rapidly; superficial ulceration of larynx, nose and nasopharynx; eruption paling; *O*, circulatory collapse; signs of bronchopneumonia; postmortem, beginning right empyema, extensive colonic ulceration, diffuse nephritis; changes in general not marked for arsenic.

Jaundice and Exfoliative Dermatitis.—This point began to interest us after the studies which led to our publication "Epidemic Jaundice as a Factor in the Treatment of Syphilis." Unfortunately, our histories are incomplete on this point. But of thirteen patients of whom we

have data, six had had jaundice of what we regard as a possibly infectious type, either before or after their dermatitis. Only one had signs of jaundice during the attack of dermatitis. We think it worth considering that a common infection possibly underlies these two processes, under certain circumstances leading to jaundice from toxic or infectious cholangeitis and, under other circumstances, to toxic erythemas and other cutaneous manifestations. It has been of interest to us to encounter, while this paper was in preparation, a patient combining both jaundice and toxic erythema, in whom arsphenamin or arsenic could not have been a factor. This case developed during a week in which two similar cases of erythema appeared on our service after single injections of arsphenamin, and while several cases of jaundice of the usual supposedly infectious type were under treatment or developing on our service. This combination case began with a chill and fever lasting twenty-four hours, and subsiding only to be followed by another chill, and fever of 103 F. Without warning, vomiting began, ending abruptly in forty-eight hours, the temperature showing a diurnal rise and fall during this and subsequent days. There was no sore throat. The cessation of vomiting was the signal for the very rapid development of marked jaundice, and forty-eight hours later a morbilliform toxic erythema appeared, which lasted three days. Morbilliform erythemas of exactly the same type had marked the reactions of two patients on the service at the same time, following their first arsphenamin injections.

EFFORTS TO ISOLATE AN ORGANISM

Necropsy in our first case terminating fatally was refused; in the second, the body had been embalmed before permission could be secured, so that we obtained nothing culturally from the two most eligible cases in our series. Two blood cultures, in a very recent case, were negative; in another case, a first culture yielded a few colonies of staphylococci and a second gave the same result. In one of the two cases of colonic ulceration, the ulcers in the rectum yielded streptococci, as has been mentioned. Cultures from the skin or from foci of infection were not attempted. The problem will require an intensive study with special technical methods. Cultures from the stool in two cases were negative with respect to typhoid and dysentery organisms. A culture from urine in one case was negative. We have, therefore, no conclusions to offer, based on bacteriologic studies. We do not believe, however, that failure to demonstrate a septicemia invalidates our theory, as a focus may sensitize without creating general infection, and even general infection without demonstration of organisms in the circulating blood is well recognized.

HISTORY OF PREVIOUS CUTANEOUS IRRITABILITY, DERMATITIS AND SO FORTH

If our suggestion to the effect that allergic susceptibility to dermatitis may be produced by the action of an acute or chronic infection, and particularly the latter, has any basis in fact, it is reasonable to suppose that a number of carriers of infection who develop cutaneous reactions to arsphenamin should give histories of cutaneous irritability and of reaction to other sources of irritation which will serve as a guide to the

TABLE 4.—HISTORY OF PREVIOUS DERMATITIS

Case	Exfoliative Reaction	Duration of Dermatitis, Days	Foci	Previous Cutaneous Lesions
12	Moderate	27	Four teeth, periapical infection grade 3	Dermatitis of thighs when first seen
3	Severe	180	Pyorrhea grade 3; periapical infection, six teeth, grade 3	Violent and extensive iodin dermatitis from local application to buttocks; no idiosyncrasy to iodids
13	Moderate	16	Five teeth with periapical infection	Severe dermatitis preceding summer, following the ingestion of iodids (?)
14	Mild	16	None	Extensive resistant eczema seven or eight months before, which was "hard to cure"
1	Severe	74	Tonsils septic; fluid pus; pus both sides of nose; chronic pelvic inflammation	Folliculitis of legs when first seen; papular dermatitis of hands resembling erythema multiforme at end of first course
15	Moderate	15	Slight acute infection in tonsils, septic tags	"Very sensitive skin"; slight dermatitis on arms and shoulders on entry
16	Severe	22 (death)	Infected impacted molar; infected antrum; fistula and rectal ulcers; infected glands	Fixed pigmentary reaction to each injection of arsphenamin
7	Mild	Several attacks 3 to 4	Pyorrhea grade 2, four teeth periapical infection; tonsils large and septic	Seborrheic dermatitis of face, neck and chest
10	Moderate	22	Infected impacted molar	Oozing eczema of the scalp and neck six months before dermatitis
17	Mild	28 (death)	Six teeth with periapical infection; septic tonsils	Acne rosacea; seborrhea of face and scalp
18	Moderate	12	Three teeth with periapical infection	Papulosquamous seborrheic dermatitis of the chest and right clavicular region
19	Mild	6	None	Itching of hands and scalp for fifteen years; dermatitis, no details given

existence of a hypersusceptibility and a useful clinical warning as to the need for special care in treatment.

A properly taken history of cutaneous lesions and accidents was obtained in only twenty-four of our thirty-three cases. Of this number, thirteen had had some form of dermatitis prior to their coming to the Clinic (Table 4).

While it may seem to be stretching a point to rate marked seborrhea as a warning of impending cutaneous hypersensitiveness, as in Case 2, we have found this point in particular substantiated more than once,

and have even, we believe, somewhat reduced the cutaneous irritability of patients toward arsphenamin by measures directed to the seborrhea as such, including especially the reduction of carbohydrates in the diet.

We have noted also that an arsphenamin dermatitis, once subsided, is not necessarily the end of the patient's difficulties with respect to dermatitis. The general cutaneous sensitiveness that underlies the explosion seems to persist, and not to be necessarily specific for arsphenamin. One patient, for example, had occasional flare-ups of dermatitis around the ankles and exfoliation of the feet thirteen months after the arsphenamin dermatitis had completely disappeared. The major explosion had apparently been only an incident in a prolonged cutaneous hypersensitiveness. The patient in Case 1 has been under observation for four years since her exfoliative reaction and during that time has had occasional sporadic outbursts of localized dermatitis, on one occasion apparently attributable to flour dust, and at others without apparent cause. The patient in Case 7 still has occasional patches of dermatitis in the axillae and groins and over the thorax, which he had before his dermatitis, and whose extension to alarming exfoliative proportions constituted the reaction which compelled us to abandon arsphenamin. Apparently, the allergic condition of the victim of exfoliative dermatitis is not as specific for arsenic or arsphenamin as a cutaneous test would suggest. For example, our experience confirms the impression of Sicard and Roger [13] on the warning which hyperirritability to iodin may convey as to the danger of an exfoliative explosion. Case 3 may be cited on this point. In another case in which a generalized dermatitis had followed what seemed to have been an iodid dermatitis, the patient responded to one small injection of arsphenamin with a moderate generalized dermatitis.

On the other hand, the patient in Case 4 did not seem especially susceptible to arsenic as such, although he exhibited a constant pigmentary reaction to arsphenamin which, to judge from its analogies in antipyrin and phenolphthalein urticaria, is a reaction of a high degree of specificity for the individual. He tolerated a high dosage over a long period without exfoliative response, and even up to the time of his death, with liver and intestinal mucosa full of arsenic, had only a partial dermatitis and very little arsenic in the skin. It would appear, then, that the specificity of dermatitis with respect to arsphenamin needs further study and may prove to be more a general and less a specific hypersensitiveness.

Two more points remain to be considered before an attempt is made to formulate a conception of the mechanism of exfoliative reac-

13. Sicard, J. A., and Roger, H.: Arsénothérapie intraveineuse et abolition du réflexe achilléen, Bull. et. mém. Soc. méd. d. hôp. de Paris **42**:585-586, 1918.

tion to arsphenamin from our observations of the last five years. These concern, first, the epidemiologic background of these reactions, so to speak, and second, the toxicity of special lots of the drugs administered in the treatment of patients who developed dermatitis.

THE EPIDEMIOLOGIC BACKGROUND OF EXFOLIATIVE REACTIONS

On this point, again, we are able to throw out only suggestions. Yet the growing importance of epidemic jaundice in many parts of the country at the present time,[14] for example, the relation of which to the treatment of syphilis we emphasized two years ago[15] as a source of error in the current estimation of the frequency of purely arsenical accidents to the liver, has, we believe, justified this form of clinical speculation. Unfortunately, the number of our cases here is too small to permit any real study of this question. Twenty-one of our thirty-three cases, or two-thirds, occurred in the Minnesota winter months of November to April inclusive, the highest proportion in March, 1922.[16] In the year by year incidence, two peaks appear, one in 1919 (ten cases) and one in 1922 (eleven cases in the first three and one-half months). In the first three and one-half months of 1922, there have occurred more cases than in any entire year preceding. In 1919, there occurred a similar peak in our incidence of jaundice; the figures for 1920 to 1922 are not as yet available.

During the postinfluenzal years, there has been a marked change in the reaction of patients to a variety of forms of treatment, and to various diseases. This matter has been repeatedly commented on informally by the staff of the Mayo Clinic. A wave of unexplained jaundice has passed through Rochester, involving first, of course, those rendered susceptible by a chemical agent such as arsphenamin, but later appearing among surgical patients, after operations having no relation to the biliary tract, and finally invading the staff itself, with sometimes fatal results in previously healthy persons.[17] Jaundice was at its height in the summer of 1921, the peak since 1919. After a period of relative quiescence, it is reappearing in milder form coinci-

14. Hiscock, I. V., and Rogers, O. F., Jr.: Outbreak of Epidemic Jaundice Among College Students, J. A. M. A. **78**:488-490 (Feb. 18) 1922.

15. Stokes, J. H.; Ruedemann, R. J., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:521-543 (Nov.) 1920.

16. It should be recalled that Ffrench thought exposure to cold the exciting cause.

17. Some fatal postoperative cases in which colonic ulceration without any basis in the surgical pathology was found also occurred at this time, in association with an obscure dysentery, and jaundice without any abnormality of the biliary tract.

dently with the worst outbreak of cutaneous reactivity that has ever been seen on our service. At the same time, outside the department, there has appeared a case of combined jaundice and toxic erythema, conforming, in general, to the characteristics of both conditions as they have been seen on this service. In certain cases and under certain circumstances, the streptococcus seems to have an association with the morbid process, but the connection is far from established. Clinically, the relation is plainer, however, The prodromes, the course of many cases and the coincidence of manifestations which are seemingly those of familiar streptococcal infections, are quite suggestive of the common instrumentality of some organism of the streptococcal type, which, as an intercurrent infection, a predisposer or an exciting cause, is altering the allergic substrate of patients and producing almost epidemic pathologic responses to irritants, stimulants and drugs in common use which ordinarily are well tolerated. In a service employing a reasonably constant and carefully controlled technic in using drugs like arsphenamin and mercury, such fluctuations in the reactivity of patients stand out in waves; when these just precede or synchronize with waves of reactivity seen in a large body of patients such as that afforded by the Mayo Clinic, they lend much weight to the conception of an infectious exciting or predisposing factor in the reactions so easily ascribed to the particular drugs in question.

RELATION OF CUTANEOUS REACTIONS TO CERTAIN LOTS OF ARSPHENAMIN USED

It remains for us to consider the question of the instrumentality of certain possibly defective or deteriorated lots of arsphenamin in the production of exfoliative reactions. We have long ago learned that the technical testing of toxicity by animal inoculation before the issuing of a given batch of arsphenamin is no final and incontestable assurance of the fact that the same preparation will not produce reactions when it is later used in man.[18] We have used consistently, with three brief well-controlled exceptions, the arsphenamin and neo-arsphenamin of the Dermatological Research Institute. We have records of the control numbers on twenty of the thirty-three cases in our series. Two suspicious batches stand out from our series, both of arsphenamin, not neo-arsphenamin. The most conspicuous and suspicious batch was administered to three patients who received injections from this lot alone, and two who received it for their last injection. These patients

18. Roth, G. B.: Keeping Qualities of Market Samples of Neo-arsphenamin while in Ampule, Pub. Health Rep. **36**:2523-2539 (Oct. 14) 1921.

Roth calls attention to the fact that such deteriorations are rare with arsphenamin, but much more common with neo-arsphenamin.

developed mild or moderate reactions. On the other hand, it must be borne in mind that a large number of patients received the same lot with undoubtedly equal frequency, without significant reaction. In fact, in the general reaction records of the section, this batch has had as good a record as any, so far as general reactions go. The second lot which aroused our suspicion was the only one received by two of our patients and formed the last injection of one other patient. Here, again, the same general principle applies. Something more than mere toxicity per se is needed to explain the fact that the same lot could be used on so many other patients without difficulty. Moreover, with the average daily list of the department approximating forty injections, it seems hardly probable, though not absolutely disproved, that any special error in mixing or any defect in technic or asepsis [19] before administration could have been responsible for these reactions. Individual details drawn from the series are as follows:

One patient who had neo-arsphenamin from three lots developed a moderate dermatitis. Neo-arsphenamin of the same lots in reduced doses was later given to another patient after a dermatitis (moderately severe) without producing any reaction; and still another patient was given neo-arsphenamin from one of these three lots after her dermatitis, without ill effect. One patient who developed dermatitis received arsphenamin from four different lots, all of which had been given at some time to patients who developed dermatitis, including the lot which we have most suspected, and developed only the mildest of toxic erythemas instead of the most serious as one would expect. We realize that none of these points are conclusive, and further investigations are being carried out with the cooperation of the Dermatological Research Institute and the Public Health Service, on the most suspicious lot, which has now been given to ten patients, who have had reactions.[20]

Theoretic Discussion of the Mechanism of Postarsphenamin Cutaneous Reactions

American and continental literature so abounds in theories of the pathogenesis and mechanism of postarsphenamin cutaneous reactions that one hesitates to add to the number. Two particularly good discussions of the theoretic aspects are available, that of Schiff,[21] and of Moore and Keidel.[4] From a combination of these two summaries, no less than five groups of theories can be collected:

19. Milian states that he has set aside ampules from an "erythematogenic" lot of neo-arsphenamin and, by using them at a later date, avoided reactions.

20. Since going to press, this lot has been subjected to careful tests, through the courtesy of Drs. Schamberg, Kolmer and Raiziss, and Dr. McCoy, and found not to be in any way deteriorated. It has a very low toxicity.

21. Schiff, P.: La gènese des érythèmes post-salvarsaniques, Ann. d. mal. vén. **16**:257-278, 1921.

1. *Bacterial Theories.*—(*a*) "Wasserfehler" and contamination of solutions with living or dead organisms (Müller,[22] Wechselmann). This was one of the early views. (*b*) Herxheimer reaction in a syphilitic process (Pinkus[23]). The destruction of organisms produces a general intoxication with cutaneous hyperemia; also an early view. (*c*) the infection theory of Milian.[24] In its original form, it distinguished between early exanthematic and late or true exfoliative reactions. The latter were due to arsenic, the former apparently to various banal infections suggesting rubella, rubeola and scarlatina as complications. Of late, Milian has apparently restated this view,[25] in a form which regards arsphenamin as having a provocative effect on latent infection, similar to the provocative action of mercury on the Vincent symbiosis in the mouth. He has observed manifestations of infection in these subjects prior to reaction. Moore and Keidel in their review accept this as possibly explanatory of the milder exanthematic reactions, but not so much of the later or exfoliative reactions.

2. *Arsenical Intoxication Theories.*—(*a*) Pistorius,[26] as long ago as 1883, showed that arsenic produces arterial dilatation by paralyzing the vasoconstrictor fibers. Hoke and Rihl[27] have maintained that an arsphenamin paralysis of splanchnic nerve terminations produces the vasodilation which explains the fall in blood pressure in toxic doses. Ricker and Knape[28] reached similar conclusions from a study of the capillaries in the living animal after arsphenamin injection. All these views are phases of the well-known vasculotoxicity of arsenic, which even the infection theory of Milian and the anaphylactic view of Moore

22. Müller, P. T.: Ueber den Bakteriengehalt des in Apotheken erhältlichen destillierten Wässers, München. med. Wchnschr. **58**:2739-2740, 1911.

23. Pinkus, F.: Ueber die hyperämischen Hautreaktionen nach Salvarsan, namentlich Frühreaktionen, Dermat. Ztschr. **18**:672-678, 1911.

24. Milian, G.: L'érythème arsenical oedémateux desquamatif, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:1055-1059 (Dec. 12) 1919; Les érythèmes arsenicaux du neuvième jour, Rev. de méd. **37**:222-235 (April) 1920.

25. Milian, G.: L'érythème scarlatiniforme de l'arsénobenzol est fonction d'infection, Ann. d. mal. vén. **15**:535-540, 1920; Biotropisme palustre par le novarsénobenzol, Ann. d. mal. vén. **17**:1-8, 1922. (The last paragraph is a particularly clear statement with which we find much to agree.)

26. Pistorius, H.: Beiträge zur der acuten Arsenikvergiftung, Arch. f. exper. Path. u. Pharmakol. **16**:188-220, 1883.

27. Hoke, E., and Rihl, J.: Experimentelle Untersuchungen über die Beeinflussung des Kreislaufes und der Athmung durch das Salvarsan, Ztschr. f. exper. Path. u. Therap. **9**:332-339, 1911.

28. Ricker, G., and Knape, W.: Mikroskopische Beobachtungen am lebenden Tier über Wirkung des Salvarsans und des Neosalvarsans auf die Blutstromung, Med. Klin. **8**:1275-1280, 1912.

and Keidel employ as the modus operandi of arsphenamin and arsenic in the excitation of postarsphenamin dermatitis. Milian [29] directs attention to the resemblance of the dermatitic syndrome to the serous apoplexy of hemorrhagic encephalitis. (*b*) The effect of arsphenamin on the suprarenal glands, as shown by Brown and Pearce,[30] Kolmer and Lucke,[31] and Hirano [32] seems to us to deserve consideration as a possible means of adapting the theory of Harris [33] on the etiology of eczema to the explanation of postarsphenamin dermatitis. (*c*) Arsenic retention due to renal injury. Wechselmann [34] and his pupil Eicke [2] have been vigorous proponents of the view that the simultaneous use of mercury and arsphenamin injures the kidney and causes an arsenic retention. In this country, Schamberg [3] has the same view.

3. *Hepatotoxic Theories.*—This element in the complex is a meeting ground of several theories. (*a*) Hoffmann [35] (1911) maintained that arsphenamin intoxication was the sequel of a perverted metabolism of the drug by a damaged liver. (*b*) Glombitza [36] considered syphilitic injury to the liver the basis of a perverted arsphenamin metabolism. (*c*) Widal [37] and his school have pointed out the effect of damage to the "proteopexic" function of the liver by arsphenamin. This impaired proteopexic function they regard as the basis of a variety of anaphylactic phenomena. (*d*) Stokes, Ruedemann, and Lemon [15] called attention to the occurrence of presumably infectious damage to the liver in the course of arsphenamin treatment.

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29. Milian, G.: Footnote 24, first reference.

30. Brown, W. H., and Pearce, Louise: Chemopathological Studies with Compounds of Arsenic. III. On the Pathological Action of Arsenicals on the Adrenals, J. Exper. M. **22**:535-543, 1915.

31. Kolmer, J. A., and Lucke, B.: A Study of the Histologic Changes Produced Experimentally in Rabbits by Arsphenamin, Arch. Dermat. & Syph. **3**: 483-514 (April) 1921.

32. Hirano, N.: Experimental Studies on the Investigation of the Nature of Anaphylactoid Caused by the Repeated Intravenous Injection of Salvarsan, Kitasato Arch. Exper. Med. **3**:1-42 (April) 1919.

33. Harris, F. G.: The Etiology of Eczema, with a Preliminary Report of Experimental Studies, Arch. Dermat. & Syph. **3**:579-592 (May) 1921.

34. Wechselmann, W.: Ueber die Verwechslung von Quecksilber—und Salvarsanexanthemen, München. med. Wchnschr. **62**:1638-1640, 1915. Loewy, A., and Wechselmann, W.: Experimentelle Untersuchungen über die Wirkung intravenöser Salvarsaninjektionen auf die Funktion der Niere, insbesondere bei bestehender Quecksilberintoxikation, Berl. klin. Wchnschr. **1**:1342-1344, 1913.

35. Hoffmann, quoted by Schiff, Footnote 21.

36. Glombitza: Spätexantheme nach Salvarsan-Natriuminjektionen; zugleich ein Beitrag zur viszeralen Frühlues, Deutch. med. Wchnschr. **43**:1452-1453, 1917.

37. Widal, F.; Abrami, P., and Iancovesco, N.: L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse méd. **28**:893-899 (Dec. 11) 1920.

4. *Anaphylactic Theories.*—These theories to be applicable at all to the observed clinical phenomena must be based on the newer colloidal conception of anaphylaxis (Bordet,[38] Doerr,[39] Kopaczewski and Mutermilch,[40] Widal,[41] Jobling[42] and his co-workers, Novy and DeKruif[43] and others) and not merely on specific antigen-amboceptor concepts. The occurrence of arsphenamin exanthems after first injections of the drug is certainly not excessively rare in our experience, and can be met only by the view that in certain individuals or under certain conditions of administration, the injection of the drug induces the "colloidoclasic" crisis of the French authors (Ravaut and Weissenbach,[44] Widal, Abrami and Brissaud[41] and Iwaschenzow[45]). In their generally accepted form, it is difficult to apply these views to the explanation of the late cutaneous accidents direct.[46] Hanzlik and Karsner[47] have pointed out the undesirability of regarding the phenomena observed as "anaphylactic" in the strict sense, and we have accordingly abandoned the term and prefer to speak rather of hypersensitiveness or allergic instability.

5. *Theories of Sensitivity or Allergic Instability.*—Moore and Keidel have ingeniously utilized a recent study by Auer[48] of the

38. Bordet, J.: Le méchanisme de l'anaphylaxie, Compt. rend. Soc. de biol. **74**:225-227, 1913.

39. Doerr, R.: Ueber Anaphylaxie, Wien, klin. Wchnschr. **25**:331-340, 1912.

40. Kopaczewski, W., and Mutermilch, S.: Sur l'origine des anaphylatoxines, Ztschr. f. Immunitätsforsch. u. exper. Therap. (Orig.) **22**:539-549, 1914

41. Widal, F.; Abrami, P., and Brissaud: Signification de l'hemoclasie, Presse méd. **1**:181 (April 3) 1920. (A remarkable exposition, with bibliography.)

42. Jobling, J. W.; Eggstein, A. A., and Petersen, W.: Serum Proteases and the Mechanism of the Abderhalden Reaction, XX, J. Exper. M. **21**:239-249, 1915. Jobling, J. W., and Petersen, W.: The Mechanism of Anaphylatoxin Formation, XV, J. Exper. M. **20**:37-51, 1914; The Therapeutic Action of Iodin, Arch. Int. Med. **15**:286-302, 1915.

43. Novy, F. G.; DeKruif, P. H., and others: Anaphylatoxin and Anaphylaxis; Ten Studies, Jour. Infect. Dis. **20**:499-854 (May) 1917.

44. Ravaut and Weissenbach, quoted by Schiff, Footnote 21.

45. Iwaschenzow, G.: Ueber anaphylaktoid Erscheinungen bei wiederholten intravenösen Salvarsaninjektionen, München. med. Wchnschr. **59**:806-808, 1912.

46. Stokes, J. H.: Atropin and Induced Anti-Anaphylaxis as a Protection Against Acute Arsphenamin Reactions, J. A. M. A. **72**:241-243 (Jan. 25) 1919. (I have also utilized these conceptions in the partial explanation of the nitritoid crisis.—Stokes.)

47. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from the Intravenous Administration of Various Colloids, Arsenicals and Other Agents, J. Pharmacol. & Exper. Therap. **14**:379-423 (Jan.) 1920; and other articles in this journal, during the same year.

48. Auer, J.: Local Autoinoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, J. Exper. M. **32**:427-444 (Oct.) 1920.

mechanism of local reaction in various tissues following sensitization by a foreign protein, to explain the mechanism of arsphenamin dermatitis. They consider that either the arsphenamin itself so changes the serum of the patient as to induce a sensitization, or bacterial proteins from foci of infection, as suggested by one of us,[49] act as the sensitizing agents. On the sensitized substrate, the vasculotoxic effect of arsphenamin reacts, repeating the xylene irritation and exudation of Auer's experiment, with a resultant response from the sensitized cutaneous cells in various grades of inflammatory reaction, ranging from mild erythema to severe exfoliative dermatitis. Moore and Keidel feel that arsenic, locally deposited in the bone-marrow following the vascular injury, may be responsible for the blood picture they find so characteristic; and they believe that the same process of local deposition of the drug in the skin excites cutaneous reaction to the pitch of dermatitis in exfoliative cases.

We venture now to offer our own conception of the factors involved in the development of cutaneous reactions to arsphenamin. A certain amount of fundamental unity seems to us to underlie them all, and to make unnecessary the differentiations based on the various types of exanthems so often found in the literature. The only type for which as yet we cannot find a place is the so-called "fixed" exanthem. We propose an allergy or hypersensitiveness, not necessarily absolutely specific for arsphenamin, as the basic fact. This allergy is perhaps at times the product, as Moore and Keidel suggest, of changes in serum or tissues induced by the injected colloidal solution of the drug. More often, we believe, the allergic instability is the result either of continued absorption of a bacterial protein from a focus of infection or of sudden liberation of such proteins following a flare-up in the focus due to arsphenamin (Milian); a phenomenon we have seen in febrile patients, with tuberculous glands for example. Sudden sensitization by acute intercurrent infection we also believe possible. It will be apparent, then, that in our basic concept we bridge the gap between infectionists (Milian) and allergists (Moore and Keidel), agreeing, in part, with both.

On the basic fact of hypersensitiveness, we may now superpose the possible effect of an impaired liver function, from arsenic as such, from chronic or acute infection or from repeated subthreshold allergic shocks (fever, and so forth, as clinical signs) following the earlier injections of the drug in a patient with an initial intolerance.[50] This impairment of hepatic (proteopexic?) function may perhaps make the body unable

49. Stokes, J. H.: The Applications and Limitations of the Arsphenamins in Therapeutics, Arch. Dermat. & Syph. **2**:303-323 (Sept.) 1920.

50. It is here that repeated severe gastro-intestinal and febrile reactions gain their import as warnings of a serious intolerance.

to deal with the protein intoxication from a focus of infection, quite as much as with the arsenical metabolites of arsphenamin. In cases associated with jaundice, this connection is especially obvious.

We further suggest the possibility that, in accordance with the observation cited, arsphenamin as such, even when properly metabolized, may cause disturbance by reducing the efficiency of the suprarenals. Then, to apply the Harris theory of dermatitis, a deficiency of epinephrin destroys the vasomotor balance in the peripheral circulation, and permits a vasodilation. This vasodilation, a frequent clinical symptom, accompanied by intense itching, which Harris suggested particularly as a sign of a deficiency of epinephrin, may then result in the sequelae suggested by the observations of Auer. Vasodilation, by permitting an increased supply of bacterial protein antigen to the sensitive cells, creates a tissue explosion with exfoliative dermatitis in the skin and inflammatory changes in other tissues.

In such a contingency as the last mentioned, arsenic in excess is not necessary. All that is needed is an arsphenamin effect on the suprarenal, which may occur early. It, therefore, meets the requirements for the observed facts of reaction after first injection, and the tendency to react after few injections before the threshold of arsenic accumulation has reached a high level. It also does away with the need for a conception of arsenic retention due to mercury, which, as we have seen, does not accord with our observed facts and comparisons.

Our theory also serves to explain the reactions of patients to whom, as in Milian's [20] case and in one of true dermatitis which we have observed, it was possible to continue the administration of the same drug for a number of injections after the onset of the cutaneous reaction. In Milian's case, the flare-ups that followed each of the earlier doses disappeared with the later and larger ones, a situation quite inexplicable if arsenic as such and its accumulation and retention are the sole, or even the principal, factor in dermatitic reactions. It is still more suggestive of the incidental rôle of arsenic in many cases that Ffrench,[51] for example, can safely recommend the practice of resuming the administration of the same brand and type of arsphenamin as soon as the patient is able to be up and around the ward again, his exfoliation just completed.

We are prepared, however, on this point, to concede the plausibility, in certain cases, of Moore and Keidel's view of the direct action of arsenic as a vasculotoxic agent and as an irritant deposited in skin and bone-marrow, when present in excess in the blood stream or improperly

51. Ffrench, E. G.: Exfoliative Dermatitis Occurring During Arsenical Treatment (with a Note on Toxic Jaundice), Lancet **1**:1262-1263 (June 12) 1920.

metabolized or accumulated. This explanation is most satisfactory in cases in which the whole picture seems arsenical, as in Latham's [52] patient (at necropsy). On the other hand, as in Case 4, the complexities of the interplay between infection and arsenic intoxication seem to suggest that the possibilities of both theories are often applicable.

We might also call attention to the value of Auer's experiment in explaining the fulminating onset of an exfoliative dermatitis following the application of external irritants, such as inunctions or tincture of iodin (Case 3 and another not reported here). They merely serve the purpose of the xylene applied to the ear of the sensitized rabbit to start the peripheral irritation and vasodilation that causes a violent response of hyperactive cells or brings "larger amounts of antigen per unit of time" to the sensitized cells to excite them to further reaction.

Summary

1. It has been our experience that cutaneous reactions to arsphenamin in general are not a function of the amount of the drug administered; and that they show a distinct tendency to occur early in the course of its administration, rather than late.

2. Comparative and direct clinical analysis indicates that postarsphenamin cutaneous reactions have no clinically demonstrable connection with the administration of mercury (except as an external irritant in inunctions); neither do they seem dependent on any renal abnormality or injury detectable by the ordinary laboratory tests. In other words, we find no clinical evidence that arsenic retention due to renal injury by mercury is a cause of arsphenamin dermatitis.

3. In a great proportion of our cases, we find evidence that chronic focal and acute prodromal or intercurrent infections form a part of the complex on which arsphenamin cutaneous reactions develop. The severity of the cutaneous reactions we have observed has stood in a rough direct relation to the extent of the infection factor.

4. We have observed serious and even fatal results associated with rapid extension and generalization of a previously mild dermatitis follow the stirring up of a focus of infection.

5. We have witnessed the immediate involution of a severe and extending dermatitis on the total extirpation of a septic focus, in one case. This favorable outcome, however, is distinctly exceptional.

6. We submit a variety of circumstantial evidence based on studies of the prodromes, the systemic symptoms, epidemiologic considerations and fragmentary bacteriologic findings, which seem to render still more

52. Latham, J. R.: Exfoliative Dermatitis Due to Arsphenamin; Report of a Fatal Case, J. A. M. A. **73**:14-16 (July 5) 1919.

plausible the conception of infection as an important part of the causative background of the exanthematic and exfoliative syndromes complicating the administration of arsphenamin.

7. We propose a theory of the mechanism of postarsphenamin dermatitis based on an allergic instability or idiosyncrasy produced either by colloidal changes secondary to arsphenamin injection, especially if accompanied by repeated reaction, or by chronic or sudden absorption of a bacterial sensitizing protein from a focal or acute infection, as the fundamental premise. On this allergy, the vasodilator toxic action of arsenic, the possible vasodilator effect of an acute shortage of epinephrin from arsphenamin injury to the suprarenal, or the vasodilator and irritative local effect of mercurial inunctions or iodin, or of other local applications, and perhaps all of them at once, react. The increased amounts of bacterial protein antigen or of arsenic as such, brought to these sites of vasodilation and irritation, still further excite the sensitized cells of the skin and other tissues to an acute inflammatory reaction. Injury to the liver from arsenic, from chronic or acute infection or from repeated allergic shock due to a series of injections in a patient already somewhat hypersensitive, may assist in the development of allergy, pervert the metabolism of arsenic, leaving it free in the blood or tissues, or interfere with the natural defense against the protein toxins of chronic focal or acute infections.

8. Our view, we believe, reconciles and combines several conflicting or partial theories and a variety of seemingly incongruous clinical facts.

INFANTILE ECZEMA AND EXAMINATION OF THE STOOLS*

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Infantile eczema occurs largely in the winter months, and it has become my custom in the treatment of the disease to instruct the mother or nurse as follows:

1. The baby is not to be taken out doors but is to be kept in a room with a southerly or westerly exposure. The heat is to be turned on, the window to be open day and night and a screen to be so arranged that neither wind nor sun shall strike the baby.

2. When the baby is to be fed or bathed, or its clothes are to be changed, it is to be taken to an adjoining warm room and returned as soon as possible afterward. Wet or soiled diapers must be changed at once.

3. Care must be taken that the baby is not too warmly dressed. Overheating congests the skin and consequently increases the itching, one of the great hindrances to a rapid cure. Rubber diapers must not be worn.

4. If the baby shows any desire to scratch, the sleeves of the night-dress must be firmly attached with a strong safety pin to the diapers. The widely advertised aluminum mits can do much damage and the stiff elbow joint cuffs do not prevent the use of the straight arm as a scratcher.

5. No soap or water should touch the eczematized skin, but the unaffected portions of the body may and should be bathed daily with tepid starch water, and, if necessary, a superfatted cold cream soap may be used.

6. No change in the diet is to be made at the first visit.

7. Night and morning, the following paste should be applied to the diseased skin, care being taken that the paste is black and never olive green: crude coal tar and zinc oxid, two parts each; corn starch and petrolatum, sixteen parts each. The paste should be buttered on with a wooden throat stick and never bandaged. Before each application, all remnants of the previous inunction should be removed with sterilized gauze wet with olive oil and the fresh ointment applied immediately afterward.

In preparing the paste, the crude coal tar should be rubbed up gently and persistently with the zinc oxid. This combination with a

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metal prevents the extraction of the crude oil from the tar. If this oil is separated from the mother substance, we have the mischievous, irritating olive-green mass which may produce a dusky erythema, pustules and possible toxic absorption resulting in headache, malaise, nausea or vomiting and pyrexia. After the crude coal tar and the zinc oxid have been well incorporated, the product should be passed through a fine sieve and rubbed up with the well-mixed corn starch powder and petrolatum. In case the scalp is involved, we omit the corn starch from the prescription. Do not hesitate to use this black ointment on the most excoriated and aggravated skin. If the eczema is a dry one, use 20 grains (1.3 gm.) of crude coal tar instead of the customary 30.

The mother should be told that the resultant black stains can be removed from the clothes by thorough inpregnation with lard, followed by washing with a pure hard soap and hot water.

These instructions are to be followed to the letter for one week, and the child is then to be examined again.

Granted that we have had the conscientious cooperation of the nurse or the mother, we expect a very definite amelioration of symptoms. If the result has been excellent, we ask for a continuation of the treatment; if the betterment has been slight, we pursue the same methods again; but if the second week proves no more fruitful than the first, we send a small amount of the last stool to a receptive pediatrician; and I believe it expedient that one man should make all of these examinations.

The qualifying adjective receptive needs elucidation. It is very evident, in Boston at least, that children's physicians are becoming skeptical about the value of stool examinations in relation to infant feeding, and this feeling is perceptibly increasing as the months go by. It is partly for this very reason that I am prompted to publish this paper, for I believe in the efficacy of this procedure in obstinate cases of infantile eczema, and I do not want to see this unquestionable benefit taken away from the victims of this harassing disease.

The following case reports represent an investigation covering a period of more than four years. Their decidedly small numbers do not indicate the comparative rareness of the disease in my practice; far from it. They betoken rather the efficiency of the treatment outlined, emphasizing, in fact, its relatively few failures; but they leave my evidence possibly unconvincing to the skeptical.

REPORT OF CASES

CASE 1.—A boy, aged 7 months, whose cheeks and forehead were somewhat red and moist, and whose stool was large and pasty, with, microscopically, a small excess of fat, was given a change in diet and was practically well eleven days later.

Case 2.—A boy, aged 21 months, developed the disease at 6 weeks of age, and the condition persisted despite the care of the physicians. Ointments, vaccines and violet light had been tried. The whole face, except the orifices, was covered with a thick mass of bloody crusts. The arms and backs of the hands presented a similar, but patchy, outbreak. At the end of six days' use of the crude coal tar, only the erythema remained; but two months later there was a relapse, and a stool examination was ordered and revealed a "remarkable" condition. The stool was sour smelling, brown and sticky, and contained a good deal of stringy cellulose material. Addition of iodin turned the whole mass black. The microscope confirmed the extraordinary excess of starch.

The mother was requested to cut down very materially the starches and cellulose and to cook thoroughly all starch given to the child. Within a few days, all eczema vanished, and there has been no recurrence of the disease since that time, January, 1918.

Case 3.—A girl, aged 13½ months, developed the disease at the age of 6 weeks. She was wholly breast-fed up to the age of 9 months. On the first visit to me, there was a quarter-size, moist, raw area over the right temple, and over the corresponding left area there were groups of somewhat moist papules. The scalp was a mass of crusts. Four weeks later, the mother reported that the crude coal tar had healed the old lesions but new ones were constantly breaking out.

The feces were large, formed and light colored. Macroscopically, many pieces of orange were visible; microscopically, there was a considerable excess of fat and a moderate increase in the starch.

A lower fat intake and a thorough cooking of the somewhat reduced amount of starch kept the disease down, but did not cure it; in fact there was a decided recurrence two years later when skin tests, construed by the early, less critical standard, revealed sensitization to twenty-three every-day articles of diet.

Case 4.—A boy, aged 6 months, who was breast-fed until 6 weeks old, developed eczema immediately after weaning, and it had continued. The cheeks were red and infiltrated and rather moist. A few isolated and coalescent papular lesions were scattered over the arms, abdomen and legs.

The feces were large, pasty and almost white—a typical "soap stool," resulting probably from a rather concentrated cow's milk mixture containing a good deal of fat and casein.

Two weeks later, the face was still congested and exhibited numerous flat, moist papules. In another fortnight, the child had gained 9 ounces (255 gm.); the face had lost its moisture and a large part of its redness, and the mother was impressed with the improvement. With his hands unrestrained, the child showed no desire to scratch.

Two months later, with the advent of the autumn, the disease seemed to show some signs of life and the child was transferred to a pediatrician for proper feeding.

Case 5.—A boy, aged 6 months, who was entirely nursed for the first eleven weeks, developed eczema one week after birth. The eruption was dry at first and then became moist. When first seen by me, the disease was more urticarial than eczematoid.

The stool was loose and watery. There were no curds, and there was no excess of fat or of starch, but there was marked evidence of the fermentation of sugar in the intestine. Lactic acid milk or buttermilk was advised but refused by the attending physician.

Three weeks later, lesions had disappeared from the body and were fading on the legs, but the face remained red and papules persisted.

CASE 6.—A boy, aged 2 months, whose brother had been a victim of eczema and also treated by me, was entirely breast-fed, and at the age of 5 weeks developed eczema. The eruption was limited to the face, which was almost solidly covered with acuminate, rather yellow, crusting, scaling papules. Boeck's wash was prescribed, and in a few weeks the eruption was largely gone; but it was soon followed by an outbreak of moisture behind the ears. This attack yielded quickly to crude coal tar, but within two weeks another attack developed. A stool examination was made and revealed pasty, dry, gray-white feces. There was no neutral fat, but there was a very large excess of total fat in the form of soaps.

Two weeks later, despite the lowered intake of fat, the eruption was still present but had altered its character completely, appearing dry and scaly on the forehead, finely papular on the cheeks and curiously exfoliative on the chest and shoulders. Was the child's diet too free from fat?

CASE 7.—A boy, aged 3 months, a breast-fed baby, developed the disease at the age of 1 month. There had been no treatment, and when first seen the cheeks were covered with pink-red, rather indefinite papules. A wash of phenol, zinc and lime water was prescribed. The child was seen six weeks later and the papules had settled down into macules. Crude coal tar was prescribed. The mother did not trouble herself much about the eruption and more or less neglected it. Three months later, in November, the child was seen again, this time with mild crusting on the cheeks and small excoriations on the forehead and elsewhere.

A stool examination revealed a loose, green movement, full of mucus and strongly acid in reaction, indicating carbohydrate fermentation. Microscopically, there was found a large excess of starch, partly in the form of large, undigested granules, partly in the form of partially digested masses.

Zwieback was eliminated from the infant's diet, and at a final visit, two weeks later, not a papule was to be seen and only a faint redness and infiltration persisted.

CASE 8.—A boy, aged 2¼ years, had developed the eruption three weeks previously. He had been receiving applications of crude coal tar of an unknown strength from another physician for two weeks. Both cheeks were fiery red and infiltrated—an indication of a too prolonged use of the coal tar or of a percentage too high.

The stool was formed, pasty and free from mucus. Microscopically, there was no excess of starch, but there was a moderate but very definite increase in the soaps. The child's fat intake was reduced and the eczema disappeared. It remained absent for three months, when a dry, scaling eczema was observed on the chin, which was constantly soaked with saliva.

CASE 9.—A boy, aged 5 months, who was breast-fed except for one bottle a day, developed the disease two months previously. Several ointments and olive oil had been prescribed by a physician. The picture was the common one of redness, moisture and crusting of the whole face and parts of the scalp. The condition was seemingly cured after one week of crude coal tar treatment, when suddenly after an application of oil of sweet almonds, a papular eruption appeared on the cheeks and forehead.

The stool was found to be loose, green, very strongly acid in smell and in reaction to litmus—a stool of sugar fermentation. The feedings were cut down to once in four hours instead of once in three, and the child was allowed

only ten to twelve minutes at the breast at each nursing. Each feeding was supplemented by an ounce (30 c.c.) of fat-free lactic acid milk. No further visits were received from the child.

CASE 10.—A boy, aged 5½ months, was bottle fed, having been nursed for only two and a half weeks. Zinc ointment and obtundia had been used, as well as Cuticura and a powder "which made the eyes water." Both cheeks and scattered areas in the scalp were red, moist, infiltrated and slightly crusting. After two weeks of crude coal tar applications, the child showed no desire to scratch and the skin appeared practically well. There was a relapse one month later, and the stool proved to be normal but high in protein, suggesting that the baby was getting very little fat, not much sugar and a good deal of protein.

Without my sanction, the mother continued crude coal tar throughout the hot summer, and when seen again in September, three and one-half months after the last visit, the baby showed minute, subacute, maculo-papules on the cheeks and several incipient comedones on the chin, all of which could be explained by the unnecessary and injudicious use of crude coal tar in hot weather.

CASE 11.—A girl, aged 13 months, who had been nursed for twelve months, developed eczema at the age of 3 months and had been treated by home physicians from the beginning of the outbreak. The eczema had grown worse since the substitution of the bottle. When first seen, there were papulo-pustules on the forehead and a paronychia of one finger. On the outer and posterior upper thighs and on the nates were large areas of minute coalescent lichenoid papules.

Three weeks later, the stool was soft, light yellow and rather foul. The microscope revealed a large excess of fat.

The child was not seen for two months. The mother reported that the skimming of the milk and the omission of butter from the dietary had cured the constipation at once. All that was visible of the previous, rather extensive outbreak was an occasional macule.

CASE 12.—A girl, aged 10 weeks, was wholly nursed for five weeks and then bottles were added. A "cradle-cap" appeared at the age of 2 months. One week before her first visit to me, the child had begun to scratch and five days later the eruption appeared. This consisted of fine papules throughout the scalp, over the forehead and about the vulva. Crude coal tar paste was prescribed.

One month later, the mother reported that the skin had been wholly well several times but that the outbreak recurred, always in a fine papular form with some moisture. The stool was yellowish-green, loose, and very acid. There was no excess of starch, but fat was present in excessive amounts, and the stool was typical of sugar fermentation. The diet was appropriately altered, and I did not see the child again.

CASE 13.—A girl, aged 11 months, who was wholly nursed for seven months, five weeks after birth developed a cutaneous outbreak, for which she was treated in two hospitals. When first seen by me, there were groups of fine papules and redness, moisture and crusting over the face and back of neck, and to a certain extent over the whole trunk. Two weeks later, the eczema was one-half to two-thirds well, but the child still scratched.

Two months later, the child was brought in again. Two weeks previously weaning had taken place, and concomitantly the skin disease had broken out again. The baby looked pale, and the scalp was buried under yellow white

scales. Stool examination revealed fat both macroscopically and microscopically. Rectification of the feeding was followed by two months of freedom from eruption and then occurred another outbreak, this time with a normal stool.

CASE 14.—A girl, aged 12 months, who was entirely breast fed for seven months and wholly weaned at eight months, developed eczema about one month after weaning. At her first visit, there were redness, slight infiltration and semimoisture on the cheeks and in the occipital region of the scalp. After ten days' use of crude coal tar all moisture and most of the redness were gone, despite the fact that the child did her best to wipe away every application. The stool was loose and contained a large excess of starch; the mother was directed to reduce the carbohydrate intake and I did not see the child again.

CASE 15.—A boy, aged 2 years, who was not weaned until 17 months old, developed eczema almost immediately after weaning. When first seen, the cheeks, backs of the hands and extensor surfaces of the arms showed dry red, somewhat abraded, indefinite areas. Treatment was wholly unsuccessful, and ten days later the previous conditions were only magnified. The stool was pasty and considerable carrot was visible to the naked eye. Microscopically, there was a moderate excess of starch.

Proper feeding produced a total cessation of the disease, which lasted for three weeks; but when rice, bread and macaroni were given the child, a recurrence of the eczema quickly took place.

CASE 16.—A boy, aged 2 years, had had the disease for several months and it had not yielded to the action of "any number" of ointments. The eruption consisted of a few areas of infiltration and dryness on the upper arms and the buttocks. Zinc jelly was tried but would not stick, and eleven days later the original areas were redder than at the first visit.

Undigested neutral fats and a small amount of fatty acids were discovered in the stool. The diet was appropriately altered and crude coal tar was prescribed. I did not see the child again.

CASE 17.—A boy, aged 6 months, who was wholly breast fed, developed eczema at the age of 6 weeks, and when first seen by me the condition was marked by redness, slight infiltration and dryness of the face and scalp. About two weeks later, the infiltration and dryness had diminished, but the child still tried to scratch. In another two weeks the eruption had practically disappeared; but, within seven days, a relapse occurred and, when seen for the third time, there were multiple excoriated papules with intervening infiltration.

The stool was greenish, loose and very acid in reaction. The microscope showed a considerable excess of fat. Sugar fermentation with secondary fat indigestion was thus revealed.

Despite explicit dietary directions, the mother had continued to give the child orange juice every morning; and, eleven days later, it was noted that the face had cleared but that the lower legs were covered with masses of grouped, excoriated papules, bound together by infiltration. The mother was again instructed as to the feeding.

After a lapse of eight months, the patient returned with a recurrence of two weeks' duration. The child was very fat and on the right cheek and on both lower legs were areas of redness and marked moisture and oozing. This time the stool was mushy, sour and acid; macroscopically, there were pieces of undigested potato; microscopically, there was a moderate excess of starch with many iodophilic bacteria—a typical stool of starch fermentation.

The starch intake was again reduced in amount and 1 pint (0.56 liter) a day of lactic acid milk or buttermilk was ordered. I did not see the baby again.

Case 18.—A boy, aged 10 months, developed the disease three weeks after birth, and it had continued despite the care of an excellent pediatrician. When first seen by me, the whole face and scalp and the trunk to a certain extent, were patchily red and raw. The mother and father were quite exhausted from the care of this long drawn out disease. After the use of crude coal tar for five weeks the child still wanted to scratch, the face was dusky red and the buttocks showed numerous, pea-size, superficial exulcerations.

The stool was pasty, rather foul, smooth, of neutral reaction, but with no evidence of sugar fermentation and no excess of starch or of fat. It was indicative of a high protein diet. Proper precautions were prescribed, and I did not see the child again.

Case 19.—A boy, aged 3½ months, a breast-fed baby, developed the eruption of eczema in the first few weeks of life. Zinc ointment, anhydrous wool fat, cotton seed and carron oil had been used before coming to me. The principal outbreak was about the genitals and buttocks, but the cheeks were red and rather dry and there was a somewhat generalized, fine, maculopapular eruption. Two weeks later, the mother said "the bad look cleared up almost at once." The redness was still evident, but decidedly diminished. The scalp was covered with fine dry scales.

Six weeks afterward, the nursing mother menstruated, and within a few days redness appeared in the folds of the baby's skin. The baby was weaned and put on a low fat, high protein mixture.

After a lapse of four months, two large papules appeared in the groin and there was a streaky, elevated redness just above the diaper line on the back. The stool, examined by Dr. W. W. Howell, showed no free fat and only a moderate amount of soap. The stool was brown and shiny, a condition suggesting the presence of starch, which was verified by the iodin test.

There was another slight recurrence of the eczema in the ensuing autumn, in the form of dry, blotchy redness about the lower face and the buttocks, while up and down the back were many small pink flat papules. The stool was examined again, this time by Dr. L. W. Hill. It was large, foul and not homogeneous, but full of gelatinous masses. The microscope revealed a great excess of undigested starch. All starch was strictly prohibited, save that in the milk, and there has been no recurrence of the disease during the last four winter months.

Case 20.—A boy, aged 2 years, developed eczema at the age of 21 months. The eruption consisted of redness and roughness of the chin and of minute papulopustules of the cheeks. The child sucked his thumb and wet the sheet in consequence. A mild protective wash was ordered but failed to cure, for, a month later, the chin was even dryer and rougher than at the first visit. The stool contained a large excess of fat, and proper directions as to the diet were given. A month later, the mother wrote that the reduction in cream, butter and eggs was followed by "an immediate disappearance of the eczema," but with the gradual resumption of these fatty foods the roughness was creeping back again.

Case 21.—A boy, aged 13 months, who had been nursed for six months and in whom the eruption had appeared at the age of 4 months, had been treated by several pediatricians. Since weaning, goat's milk had been the staple article of diet. The forehead, wrists and bends of the knees were red, infiltrated and wet. The cheeks showed a few small papules. The child scratched incessantly and vigorously during his whole visit.

TABLE 1.—TABULATION OF CASES

Case and Sex*	Age	Breast-Fed	Age at Which Disease Appeared	Situation	Type of Lesion	Stool Examination	Results
1 ♂	7 mo.	.....	.....	Cheeks, forehead	Redness, moisture	Fat +	Prompt recovery
2 ♂	21 mo.	.....	6 wk.	Face, arms, hands	Bloody crusts	Starch +++ cellulose +	Prompt recovery
3 ♀	13½ mo.	9 mo.	6 wk.	Temples, scalp	Moisture, moist papules	Fat ++ starch +	Amelioration
4 ♂	6 mo.	6 wk.	6 wk.	Cheeks, arms, abdomen, legs	Redness, moisture, papules	Fat +	Amelioration
5 ♂	6 mo.	11 wk.	1 wk.	Body, legs, face	Moisture, papules	Sugar +	Treatment by feeding refused
6 ♂	2 mo.	2 mo.	5 wk.	Face	Papules, moisture	Fat +++	Changed from wet to dry
7 ♂	3 mo.	3 mo.	1 mo.	Cheeks	Papules, moisture	Starch ++	Prompt recovery
8 ♂	2¼ yr.	.....	2 yr., 2 mo.	Cheeks	Redness	Fat +	Amelioration
9 ♂	5 mo.	5 mo., with 1 bottle a day	3 mo.	Face, scalp	Redness, moisture, papules	Sugar +	Recovery ? †
10 ♂	5½ mo.	2½ wk.	.....	Cheeks, scalp	Redness, moisture	Protein +	No improvement
11 ♀	13 mo.	12 mo.	3 mo.	Forehead, thighs, buttocks	Papulo-pustules, papules	Fat ++	Recovery
12 ♀	10 wk.	5 wk.	2 mo.	Scalp, forehead, vulva	Papules, moisture	Fat ++ sugar ++	Recovery ?
13 ♀	11 mo.	7 mo.	5 wk.	Scalp, face, neck, body	Redness, moisture, papules	Fat +	Recovery and relapse
14 ♀	12 mo.	7 mo.	9 mo.	Cheeks, scalp	Redness, moisture	Starch ++	Recovery ?
15 ♂	2 yr.	17 mo.	7 mo.	Cheeks, hands, arms	Redness, dryness	Starch +	Recovery
16 ♂	2 yr.	.....	1¾ yr.	Arms, buttocks	Infiltration, dryness	Fat +	Recovery ?
17 ♂	6 mo.	.....	6 wk.	1st attack: Face, scalp, legs	Infiltration, dryness, papules	Fat ++ sugar +	
				2d attack: Cheeks, legs	Redness, moisture	Starch +	Recovery ?
18 ♂	10 mo.	.....	3 wk.	Face, scalp, trunk	Redness, moisture	Protein ++	Recovery ?
19 ♂	3½ mo.	3½ mo.	2-3 wk.	1st attack: Cheeks, genitals, buttocks, groins	Dryness, fine maculo-papules	Fat + starch +	
				2d attack: Face, buttocks	Redness, dryness, papules	Starch ++	Recovery
20 ♂	2 yr.	.....	21 mo.	Chin, cheeks	Redness, dryness, papulo-pustules	Fat ++	Recovery
21 ♂	13 mo.	6 mo.	4 mo.	Forehead, cheeks, wrists, knees	Redness, infiltration, wetness, papules	Starch ++	Recovery ?
22 ♂	3 mo.	2-3 wk.	.....	Cheeks	Redness, moisture	Fat +	Amelioration

* In this column, ♂ indicates male, ♀ female.

† In my practice it is not the custom for patients to return when they are well or approximately so. The great majority of my local patients seem to report so long as results are unfavorable and cease to return when a cure is imminent.

After the use of crude coal tar for seven weeks, the skin appeared very much improved. The diseased areas were much smaller and distinctly less infiltrated, but the child was still scratching. The stool was small, well formed and light yellow. Microscopically, there was a large excess of starch. Proper feeding was instituted, and I did not see the child again.

CASE 22.—A boy, aged 3 months, who was breast fed for a few weeks only, gave a history of eczema and asthma in various members of the family. When first seen, the baby's cheeks were red and somewhat crackled, following the application of a drying wash recommended by a pediatrician. Four days' use of crude coal tar very nearly cured the skin, and the baby was not seen again for six months because of absence from town. The eczema, however, had persisted in a mild, uneven manner throughout the summer. On returning to town, an exacerbation occurred and the face became decidedly moist. A stool examination by Dr. W. R. Sisson disclosed a very definite excess of fat.

TABLE 2.—SUMMARY OF CASES *

	Cases
Sex: Males, 17; females, 5	
Age When Disease First Developed:	
1 week	1
2-3 weeks	2
4 weeks	1
5 weeks	2
6 weeks	4
2 months	1
3 months	2
4 months	1
5 months	1
6 months or more	5
Situation of Lesions:	
Face	22 (all)
Scalp	8
Legs	6
Arms	5
Trunk	4
Buttocks	4
Hands	3
Type of Lesion:	
Moisture	16
Erythema	14
Papules	14
Dryness	6
Stools:	
Abnormal fat	13
Abnormal starch	9
Abnormal sugar	4
Abnormal protein	2
Results following Correction of Diet:	
Recovery	7
Assumed recovery	8
Improvement	4
No success	1

* In the fifteen recorded cases in which the babies were breast-fed, ten were nursed less than six months.

The fat intake was reduced in amount and the eczema improved, but did not entirely abate. After a two and one-half months' period of comparative quiescence, there was a sudden flare up when the baby's Holstein cow "dried up" and by mistake Guernsey milk was substituted.

I believe it a wise procedure to have one man make the stool examinations, for in this way the work is standardized. I believe it wise to ask the cooperation of a pediatrician who has faith in the value of stool examinations. For these reasons, I have sent the stools, whenever possible, to Dr. Lewis Webb Hill.

CONCLUSIONS

1. Proper use of crude coal tar paste, properly prepared, with the most conscientious regard to proper general precautions will cure and cure promptly the great majority of cases of infantile eczema treated in private practice.

2. The number of failures to cure promptly under the foregoing conditions during the last four years and more have been relatively small—so small that the ensuing deductions may be unfortunately and of necessity comparatively valueless.

SUMMARY (OBSTINATE CASES)

1. Boy babies predominated, more than three to one.

2. All babies were breast fed, two thirds for six months or less. In several instances eczema appeared soon after the cessation of nursing.

3. These babies were not born with eczema, not even with "cradle caps." The disease seems to appear at all ages, but there were relatively few cases before the age of 1 month, and in nearly a quarter of them it did not appear until six months had elapsed.

4. The face was the favorite seat of the disease in 100 per cent. of the cases. The scalp follows, a poor second. It is surprising to note the comparative infrequency with which the diaper region is attacked.

5. The eruption is essentially a moist one, simple erythema or papulation also occurring in the greater proportion of the cases. There are dry types, but they total a small third.

6. Abnormal stools seemingly accompany every obstinate example of infantile eczema. Excessive fat occurs in 60 per cent.; excessive starch in 40 per cent.; excessive sugar in 20 per cent., and excessive protein in 10 per cent.

7. Rectification of the diet was attended with distinct success in the great majority of the cases.

My object in making this study was to prove not only that the examination of the stools in the recalcitrant cases of infantile eczema is a justifiable method of procedure but also that such an examination would prove of value in treating these cases which had refused to disappear under the proper use of crude coal tar. Although my records of these cases are numerically surprisingly few, I believe they justify my firm belief that abandonment of these examinations, now increasingly advocated by the pediatricians, is a misfortune and should be combated by dermatologists.

When, as seemingly proved by these records and by these stool examinations, every case of obstinate infantile eczema is accompanied by an abnormal stool; and when, apparently, rectification of the child's

diet, based on these findings, and conscientiously followed and pursued by the mother or nurse, result in a cure or an apparent cure or at least a distinct improvement in practically every case, then, I say, it seems incumbent on dermatologists to adopt these methods of procedure and to strive to prevent pediatricians from decrying them.

DISCUSSION

Dr. Richard L. Sutton, Kansas City: I feel that I have learned more about this disorder in infants from Dr. White than from all other sources put together. I am glad that in his present paper he has emphasized the importance of careful stool examinations by some one who is not only skilful, but who is also sufficiently interested to see that the work is carefully and conscientiously carried out.

One point more: I should like to recommend a cleansing solution which we have found extremely valuable for use in these cases. I refer to Dr. Pusey's tragacanth emulsion. The formula that I employ consists of powdered tragacanth, 1 dram; glycerin, phenol, and oil of bergamot, each, 5 minims; olive oil, 4 ounces, and water, sufficient to make 1 pint.

Dr. Harry P. Towle, Boston: In Dr. White's figures, 60 per cent. of the cases have fat, 40 per cent. starch and 20 per cent. sugar. That is particularly interesting. We do find an occasional sugar intolerance, sugar anaphylaxis, but my figures are rather lower than his.

One point about applications: In certain types of cases, we can handle the eruption with impunity; in others, the skin is so hypersensitive that, it has struck me, there should be as little manipulation as possible. In such cases, it is my custom to apply the crude coal tar without rubbing and then to powder with starch, making a sort of mortar. This is left in place for seventy-two hours, when it is soaked off with oil. This seems to be more helpful than the more frequent removal. I cannot too highly recommend this treatment to practitioners, provided they can get a properly prepared product. It varies markedly in the hands of different druggists and requires care in preparation.

Dr. Harold N. Cole, Cleveland: I should like to recommend in addition to the crude coal tar preparation the value of very weak doses of roentgen ray. It has a wonderful effect on some of these children, especially in stopping the pruritus.

Dr. Walter J. Highman, New York: I think one of the most hopeless things in infantile eczema, particularly in breast-fed infants, is the attempt we make to incriminate a diet that is physiologically and biologically so normal that it is difficult to conceive of its ever becoming a pathologic agent. The reports on breast-fed infants having this type of skin reaction vary so greatly with every school that there is no possible unaninimity of view. I have noticed that infantile eczema seems to be worse in cold months, and it has occurred to me that very possibly the entire condition will prove to be a reaction to wool which children wear in the cold season. That at least is something extraneous and something we may be able to apply in handling the disease. It seems difficult to believe that breast-fed infants may develop skin disease as a result of their diet when they are otherwise normal, and on the only food meant for them.

Dr. J. Frank Schamberg, Philadelphia: I do not know the experience of others, but in my own experience the treatment of infantile eczema is in a general way disappointing. When I come into consultation with pediatricians,

I find that I shift the burden to them and they shift it back to me, and in the end we find that a very high percentage of these cases persist, commonly throughout the first year of the child's life. I have the distinct impression that the greatest period of incidence of eczema during child life occurs when the child is on a purely milk diet, and that the eczema tends to subside when the child is put on other food than milk. The question as to whether the eczema is caused by an excess of protein or fat or some sensitizing agent in the milk of the mother, or whether the cause is intestinal, will doubtless vary in different cases. It has struck me that the best way to study this fundamentally would be to devote a ward in a hospital to the treament of infantile eczema, using in one group a low protein diet, in the second a desaccharated milk and in a third a fat-free milk diet, and noting the effect on the eczema. In other cases intestinal poisons due to faulty intestinal digestion might be operative. The findings of Dr. White might be correlated with such an assumption.

Some years ago, I had one of my assistants secure the milk of mothers of children coming in with eczema, who were maternally fed. At that time, I had the opinion that an excess of fat in the milk was responsible in such cases for the eczema, but after examining a dozen or more cases found the fat content was not above normal. I think many of the eczemas are not due so much to fat content in the bowel as to the formation of toxins. I have been interested for some time in the subject of intestinal toxemia, and find that from 5 to 10 per cent., nearer the latter figure, of my private patients who come in with skin affections have other symptoms of intestinal toxemia. They present symptoms which are often removed with change of diet, which likewise very often brings about a disappearance of the eruption. Unfortunately, pathologic chemistry has not advanced to a point where we know much about intestinal toxemia. I am convinced that certain substances that will prove to be as definite as alkaloids are formed in the bowel and produce mental and physical depression, inability to concentrate, etc., and, in many instances, skin disease such as general pruritus, certain types of erythematous eczema and the like. At present, we are carrying out a research on this subject and have a physiologic chemist who is devoting all his time to this work and a bacteriologist who does nothing but examine the feces in these cases, to determine the bacterial flora; he determines the number of different colonies of bacteria and their toxicity. That the bacterial flora may be changed by diet is now well substantiated. We are attempting to demonstrate the toxicity of intestinal bacteria by experimental injections into animals. This work is still young, but I hope we may, at the next meeting, be able to present a paper on the relation of intestinal toxemia to diseases of the skin.

Dr. Howard Fox, New York: Like Dr. Schamberg, I often feel discouraged at the results of treatment in infantile eczema. There are certainly many cases that are not radically cured by either the dermatologists or pediatricians. In one patient of fifteen months, I obtained very satisfactory results by roentgen-ray treatment, while in others I have been greatly pleased with the use of crude coal tar ointment as suggested by Dr. White.

Dr. Samuel E. Sweitzer, Minneapolis: In Minneapolis, the pediatricians are so satisfied with the crude coal tar ointment that they no longer need the work of the dermatologist in the average case.

Dr. Shannon has been doing some work with the iodids in checking up the diet of the mothers. He has a series of quite a number of cases in which he has taken the mothers' food and by withdrawing certain articles of diet from the mother has corrected the condition of the baby.

DR. HARRY E. ALDERSON, San Francisco: I recently had a patient with infantile eczema which was apparently due to home brew. The mother consumed quantities of home-made beer and there was little doubt about the relationship between this and the eczema of the infant, because the withdrawal of the beer was followed by prompt subsidence of the lesions, which before had been very persistent.

DR. CHARLES J. WHITE, Boston: I am rather surprised at Dr. Highman's remarks. I had supposed that it was more or less an accepted fact that what the mother ate influenced the child. I learned this fact very early in my own experience. My oldest child was born in Vienna, and there it was the custom to give the mother as much beer as she could take, and throughout those weeks in Vienna I walked the floor for hours, patting my boy's back trying to rid him of gas produced by the beer.

Eczema I look on merely as an eruption on a sensitized skin. We all know that every one, whether infant or adult, has more eczema in winter than in summer.

I congratulate Dr. Schamberg on his living in Philadelphia. In Boston, where they try things on dermatologists first, and where, some years ago, they took the treatment of syphilis away from us, they are trying to take away eczema; and if he can hold the cases he should do so and not pass them on to the pediatrician. I agree with Dr. Schamberg that other diseases or other manifestations of disease are to a certain extent due to intestinal intoxication.

I should like to ask Dr. Towle whether he used this preparation pure or in a 5 per cent. paste.

DR. HARVEY P. TOWLE, Boston: I have used it in both ways in some cases. When they are at their height, with marked edema, I find the pure crude coal tar is more efficacious than the paste. That is an alarming statement to those who have not seen it so used, but properly prepared it is not irritating. If there is a great deal of serum, I use a powder to keep the skin dry.

TREATMENT OF ARSPHENAMIN DERMATITIS AND CERTAIN OTHER METALLIC POISONINGS*

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For years, our books on toxicology have ingnored the fact that the nonmetal sulphur is a precipitant for a whole group of metals, such as arsenic, mercury, lead, bismuth, zinc and copper.

Many derivatives of these metals are used in the treatment of disease, or taken by mistake or with suicidal intent. Formerly, a direct precipitant was not used as a neutralizing agent, but now the procedure in handling these cases has become quite simple.

Obviously, pure sulphur cannot be used, but its derivatives can: calcium sulphid, calcium sulphite and sodium thiosulphate. The last is the preparation of choice because, (1) on account of its great solubility, it can be given in concentrated solution; (2) it is absolutely nontoxic up to 2 gm., given intravenously, and (3) its chemical action is rapid. The other two preparations are to be discarded, because of their comparative nonsolubility or their toxicity.

Sodium thiosulphate converts all of these toxic metals into the nontoxic insoluble sulphids; therefore, it should be the chemical of choice in the treatment of arsenical poisoning, acute or chronic: mercurial poisoning, acute or chronic; stomatitis of mercurial origin; acute lead poisoning; bismuth poisoning, etc. We will confine this paper, however, to the discussion of treatment in the first two mentioned, by use of sodium thiosulphate given intravenously and by mouth.

Two facts must be kept in mind: the chemical must be pure and it must be sterile. (A. A. Metz Laboratories, New York, kindly furnished us the chemical in air-tight sterile ampules, in the same size doses as the arsphenamin preparations). The technic of administration is the same as that of neo-arsphenamin (concentrated method).

Given a typical case of arsphenamin dermatitis, the administration is as follows: 0.3 gm. of sodium thiosulphate is given intravenously; the following day, 0.45 gm.; the third day, 0.6; the fourth day, 0.9; the sixth day, 1.2, and the eighth day, 1.8. This is usually sufficient for the severe case of arsenical dermatitis. Following the first dose, the redness, edema and serous exudate become lessened. The dry,

* Read at the Forty-Fifth Annual Meeting of the American Dermatological Association, Washington, D. C., May 2-4, 1922.

desquamating stage is reached on the fourth to the tenth day. The entire course of the condition is shortened from three to six months to as many weeks.

This method of treatment shows even more remarkable results in the cases of mercurial poisoning. Given a case of acute mercuric chlorid poisoning, with severe abdominal pain, bloody stools, albuminous urine and even unconsciousness, the same methods are followed, in a general way, as in arsenical poisoning. After the first dose, the pain is markedly relieved; after the fourth dose, the patient is practically well. Along with this treatment, 15 gm. of sodium thiosulphate in 480 c.c. of water are given by mouth, followed by 1 gm. in solution, three times daily.

We believe that the use of the method herein described is a great step forward in the treatment of metallic poisoning.

The use of sodium thiosulphate in the treatment of arsenical dermatitis was first described by P. Ravaut.[1]

Let us first take up the factors which predispose a patient to arsphenamin poisoning. The prime factor is the failure to eliminate the arsenical products. It is our belief that the organ responsible for this failure is the liver and not the kidney. In support of this argument is the fact that when these cases have come to necropsy, it is not the kidney, but the liver which is most affected. All stages of liver degeneration are found, ranging from cloudy swelling to massive degeneration. True, the kidneys show some change, but in no such degree as shown in the liver. Therefore, the deduction can be drawn that the liver has failed to do its proper work in breaking up and eliminating the arsphenamin. We are conducting animal experiments at present, in an attempt to prove this point. On the other hand, it is a well-known fact that the kidney and lower bowel are the most susceptible tissues in the body to mercurial poisoning, as proved by the presence of blood in the stools and urine, and the rapid destruction of the kidney tissue following the ingestion of toxic doses of the mercurial salts.

PATHOLOGIC FINDINGS IN ARSPHENAMIN DERMATITIS

Urine.—The urinary findings are not a deciding factor in this condition. The specific gravity is usually somewhat high, from a trace to a moderate amount of albumin, and not constant; an occasional cast and red blood cells.

Blood.—Examination reveals: leukocytosis, 12,000 to 18,000 with a high percentage of eosinophils (from 5 to 25 per cent.); blood urea, low; blood sugar, unchanged.

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1. Ravaut, P.: Presse méd. **28**:73 (Jan. 28) 1920.

Serologic Reaction.—The Wassermann reaction is usually negative when the patient has recovered from the dermatitis.

Arsenic Content.—The presence of arsenic in the blood, urine and feces has been carefully worked out by others.

In contrast, the urinary findings in mercurial poisoning are: suppression of urine; small amount; smoky color; moderate to large amounts of albumin; numerous coarse, fine, granular and epithelial casts, also red blood cells. Therefore, we believe that certain conditions which involve the eliminating organs, especially the liver, act as a contributing factor in the production of arsphenamin dermatitis.

1. Acute infections, occurring during or shortly after intensive treatment. In five of our most severe cases, such an infection took place. One had an acute follicular tonsillitis; one a severe furunculosis; one an extensive abscess between the muscles of the thigh; one bronchopneumonia, and another the flaring up of a chronic pyosalpinx.

2. The intravenous use of arsenic and mercury during the same course of treatment, one having more effect on the liver and the other more effect on the kidney.[2]

3. Pathologic conditions existing in the patient prior to the administration of arsphenamin, such as cirrhosis of the liver, gumma of the liver, icterus, chronic perihepatitis and hepatitis, malignancy and pernicious anemia.

4. A previous arsphenamin dermatitis. A recurrence makes its appearance at once, even if the drug is given after a period of one year or more. A case illustrating this point:

Miss A., aged 18 years, who had secondary syphilis, was given four doses of arsphenamin, 0.6 gm. each, one week apart during the year 1920. She developed a rubelliform rash, with edema of the eyelids, which slowly progressed to extreme edema of face, arms and legs; in fact a severe case of arsphenamin dermatitis, from which it required six months to recover. She received no treatment for nine months. She was then given 0.45 gm. neoarsphenamin, with the recurrence of all symptoms, and even in a more severe form.

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2. Strathy, G. S.; Hannah, B., and Smith, C. H. V.: Delayed Arsenical Poisoning, Lancet **1**:802-807 (April 10) 1921. Shamberg, J. F.: Clinical Commentary on Studies of Histologic Changes in Organs Induced by Arsphenamin, by Neo-Arsphenamin and by Mercury, Arch. Dermat. & Syph. **2**:571 (April) 1921. Kolmer, J. A., and Lucke, B.: Study of Histologic Changes Produced Experimentally in Rabbits by Arsphenamin, ibid. **3**:483 (April) 1921; Study of Histologic Changes Produced Experimentally in Rabbits by Mercurial Compounds, ibid. **3**:531 (April) 1921. Moore, J. E., and Keidel, A.: Dermatitis and Allied Reactions Following Arsenical Treatment of Syphilis, Arch. Int. Med. **27**:716 (June) 1921. Smith, cited by French, E. G.: Lancet **1**:262 (June) 1920

5. Large doses of arsphenamin repeated at too frequent intervals and over too long a period.

6. Toxic substances in the arsphenamin: (*a*) those not removed by the manufacturer; (*b*) oxidized products due to faulty container; (*c*) unfiltered solution.

7. Faulty technic, such as toxic substances in the vehicle.

Prodromal symptoms in arsphenamin dermatitis, in the order of their appearance: (*a*) itching and burning of the palms and soles (nearly every patient will note these symptoms and voluntarily speak of them), the dermatitis usually following after the next injection; (*b*) the appearance of a rubelliform eruption, with edema of the eyelids and severe diarrhea, this occurs within twenty-four hours after the injection; (*c*) loss of weight and extreme nervousness; (*d*) albumin and casts in the urine; (*e*) low urea content of the blood.

REPORT OF CASES

Of these cases of severe arsphenamin dermatitis, four were due to neo-arsphenamin, one to solution of potassium arsenite (Fowler's solution) and one to sodium cacodylate. In all of these cases there were practically the same signs and symptoms, and in all there was complete recovery.

CASE 1.—Miss M., aged 49, whose condition was diagnosed as tertiary syphilis, and whose Wassermann reaction was four plus (alcoholic extract), presented necrosis of the bones of the nose and gumma of the breast, which had undergone malignant degeneration. She was a large, fleshy woman. She was given four doses of neo-arsphenamin, 0.9 gm. each, five days apart. Three days after the last dose, there developed a severe macular rash and edema of the lower eyelids, which rapidly progressed until, four days later, the entire body was red, and the face, neck, arms and legs were greatly swollen. There was a serous exudate of such severity that several thicknesses of gauze were quickly saturated. Three tenths of a gram of sodium thiosulphate was given intravenously and the following day, 0.45 gm., with rapid disappearance of signs and symptoms. She was able to resume her work in ten days. Four days later there was a recurrence of all symptoms in even a more severe form. She was given 0.45, 0.6, 0.9 and 1.8 gm. on successive days, with complete recovery in six weeks. She is now in excellent condition.

CASE 2.—Mr. W., aged 59, presenting a case of pernicious anemia and tertiary syphilis, with Wassermann reaction four plus, was given solution of potassium arsenite (Fowler's solution), eight drops at a dose, until a total of 30 gm. was given. This was followed by two weekly doses of silver arsphenamin, 0.2 gm. each. One week later, the same symptoms appeared as in the foregoing case. He was given 0.3, 0.45, 0.6, 0.9 gm. of sodium thiosulphate on successive days. All symptoms disappeared; patient left the hospital in two weeks, completely recovered, and has remained so, except for pernicious anemia.

CASE 3.—Mrs. B., aged 38, was given sodium cacodylate, intravenously, twice a week for a period of more than two months. She developed edema of the eyelids, arms and legs, with marked thickening of the palms and soles.

She was given four injections, 0.45 gm. each of sodium thiosulphate in two weeks, with rapid disappearance of all signs and symptoms.

These three cases are given as fair illustrations of the rapid and beneficial action of this form of treatment.

In the paragraph on contraindications of the use of arsphenamin, we mentioned a previous reaction. We will here report four cases, three an exception to the rule, and one presenting a recurrent dermatitis.

CASE 4.—Mrs. C. gave a diagnosis of late secondary syphilis, with severe headaches. The cerebrospinal fluid revealed marked meningeal involvement. She was given 0.3 gm. of neo-arsphenamin, intravenously, but the headaches were not relieved. Three days later, she was given 0.45 gm. of neo-arsphenamin. That evening she became nauseated and had chills and a temperature of 104 F. The temperature persisted for ten days, ranging from 102 to 104 F. The right upper apex showed signs of lobar pneumonia. Coincident with the temperature, the patient developed a rubelliform eruption, which gradually fused into the scarlatiniform type, with edema of the eyelids, arms and legs. She was immediately put on sodium thiosulphate by mouth, 1 gm., three times a day. At the end of ten days, there was desquamation, and the patient had no further trouble. Injections of mercuric chlorid in a fatty base were given at four-day intervals for two months, when the headaches again returned with their original intensity. Sodium thiosulphate, 5 grains (0.3 gm.), three times a day, had been given all this time. Because of the gravity of the case, it was decided to give arsphenamin again. Eight injections of neo-arsphenamin, from 0.2 to 0.45 gm. at five-day intervals, were given, with no untoward results or signs of a dermatitis. The patient became markedly paretic, one year later.

Dr. Ralph Hissem of Wichita, Kan., reported two cases to us, both patients developing severe dermatitis after one course of arsphenamin. He followed out the sodium thiosulphate treatment, and was able to continue the course with arsphenamin without the reappearance of dermatitis.

CASE 5.—Mrs. D., aged 45, with a diagnosis of tertiary syphilis (brain meningeal type), who was given six injections of arsphenamin, 0.6 gm. each, one week apart, developed an intensive dermatitis, with loss of hair and toe and finger nails, which lasted for six months. This occurred in 1916. On an average of twice a year, up to 1920, she had a rather severe exfoliating dermatitis, occurring about the site of injection. She was then placed on sodium thiosulphate, 15 grain (1 gm.) doses, three times a day, and has not had a recurrence.

While the beneficial action of sodium thiosulphate is most remarkable in arsenical dermatitis, it is even more so in the treatment of acute mercurial poisoning and mercurial stomatitis.

Ampules of this preparation should be kept in all emergency hospitals for such cases of acute poisoning. Workers [3] have reported mercurial cases successfully treated with calcium sulphid, given intravenously and by mouth, but we prefer the thiosulphate for reasons already stated.

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3. Wilms, J. H.: J. Lab. & Clin. Med. **2**:445 (April) 1917.

CASE 6.—Mrs. G., aged 29, who was eight months pregnant, took four 7½ grain tablets of mercuric chlorid with suicidal intent. Within one hour, she was suffering from abdominal pain, with constant desire to stool, and stools bloody. She was seen four hours after taking the poison. The urine showed albumin, numerous casts and red blood cells. She was given 15 gm. of sodium thiosulphate by mouth and 0.45 gm. intravenously. The pain and desire to stool became very much less. Eight hours later, she was given 0.9 gm., and the next morning, 0.45 gm. The urine was clear in one week, and the patient made a complete recovery, without even aborting. This case we consider most remarkable. (The patient was treated by Dr. C. H. Hunt of Kansas City, Mo.)

CASE 7.—Mr. H., who was receiving injections of mercuric salicylate, presented himself at the clinic with swollen, spongy and bleeding gums and intense pain. He was unable to sleep. This was a typical case of mercurial stomatitis. He was given 0.45 gm. of sodium thiosulphate intravenously at two p. m., and that night was able to sleep. Two more injections were given on alternate days; and, at the end of a week, the patient had completely recovered, although there was considerable retraction of the gums. We have had five other cases which have responded to this treatment.

CONCLUSIONS

1. Sodium thiosulphate given intravenously and by mouth rapidly shortens the course of arsenical dermatitis.

2. It is a successful neutralizing agent for acute and chronic mercurial poisoning.

3. To secure the best results, it must be given intravenously.

4. In its pure form, it is nontoxic up to 2 gram doses.

5. Certain conditions which impair the liver or kidneys are predisposing factors in the production of arsphenamin dermatitis.

6. Certain warnings are often given which, if carefully observed and heeded, will prevent its appearance.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. STOKES AND CATHCART, GASKILL, AND MC BRIDE AND DENNIE

DR. JAY FRANK SCHAMBERG, Philadelphia: I am sure we are all indebted to Drs. Stokes and Dennie for bringing up the important question of the treatment of arsphenamin dermatitis. This complication is more frequent at the present time than heretofore, doubtless because of the extended use of the arsenical drugs in this and other countries. We were more or less accustomed in the early days to hear of encephalitis as the most feared complication of arsphenamin administration. We are now hearing less of this and more of dermatitis and hepatic accidents, some terminating fatally.

In the work carried out by my associates, Drs. Kolmer and Lucke, the fact was clearly established that the arsphenamins produce dominant structural changes in the liver; whereas, the changes after mercury administration were chiefly in the kidney. Relatively small doses of mercury appear to be capable of inducing distinct structural changes in the kidney. They are such, however, as commonly occur after certain infectious diseases, and restitution ultimately takes place, unless the damage is too great.

I have expressed the opinion that the conjoint use of vigorous doses of mercury during arsphenamin treatment was a factor in the production of arsphenamin dermatitis. For the last five years, we have given almost straight arsphenamin or neo-arsphenamin treatment in our clinic, and we have had a remarkable record with regard to arsphenamin dermatitis. After 25,000 treatments, we have had no more cases of dermatitis than could be numbered on the fingers of one hand, and we have never had a severe case. We have had about the same number of cases of mild jaundice. I was struck by the difference in the incidence of these compliations in our clinic and in clinics in which mixed mercurial and arsenical treatment is employed.

Most interesting and pertinent is the report of fifty-eight cases of delayed arsenical poisoning observed in an English war hospital by Strathy, Smith and Hannah. Symptoms developed on an average of forty-five days after treatment. Eight of the cases were fatal. Thirty-nine patients were admitted for jaundice and eight for dermatitis. In two cases, dermatitis was followed by peripheral neuritis. The average total amount of arsphenamin given the patients was relatively small. All of the patients received intramuscular injections of mercurial (gray) oil at the same time as the arsenical. A few of the patients showed slight symptoms of mercurial poisoning, and the authors regarded the mercury as a predisposing factor. They added that if the kidneys were damaged by mercury, the elimination of arsenic would be delayed.

If arsenic is retained in the liver or other tissues for an excessively long period, it might undergo oxidation and might ultimately be split off from the benzene ring. Unfortunately, nothing definite is known concerning the final date of arsenic retention in the system after the administration of arsphenamin. The liver is the great depository of metallic substances that are injected into the blood stream, and in an incredibly short time after the injection of arsphenamin, the drug disappears largely from the circulating blood and is deposited in the liver and other organs. It is quite comprehensible that if one interferes with the renal excretion of arsenic, a larger amount will remain in the liver and for a longer period of time. This may lead to injury of the hepatic cells, ending in necrosis, as has been experimentally demonstrated by my colleagues; and ultimately fatty degeneration might take place.

The cause of dermatitis after arsphenamin administration is still obscure. I believe we all will, ultimately, be compelled to modify our present opinions. Our present views are based on laboratory work and clinical data, but they are not sufficiently positive to permit any one of us to commit himself to a definite dogma.

In regard to Dr. Dennie's excellent paper I would say that my colleagues and I have had the impression that sulphur tends to lessen the toxicity of the arsphenamin molecule. Although sulphur has no place in the structural formula of arsphenamin, traces of it will always be found on analysis. It is a little difficult to understand how structural damage which has already been done by an injected drug can be repaired by the introduction into the blood of a substance like sulphur, even though the latter exerted a reducing effect.

With regard to mercury, this drug acts quickly on the cells of the kidneys and produces destructive changes. Unless treatment was applied with great promptness, it is difficult to conceive how the damage could be prevented or repaired. We will have to await more extended clinical trial before a judgment can be given concerning its actual value.

Dr. E. Wood Ruggles, Rochester, Minn.: I have had some unpleasant experiences with arsphenamin, after two or three years with practically no

reactions at all except that, in perhaps half of the cases in which patients come in with a secondary infection, with no previous treatment, there is a moderately severe reaction; after the first injection, not subsequently.

April 10, 1922, I administered arsphenamin to three people, using 0.4 gm. of Serial No. 6128, in the afternoon, and in the evening 1 gm. of Serial No. 4685. The first dose was administered to a woman; of the 1 gm., 0.5 was given to her husband, and 0.5 to another patient. These were the fourth injections in all cases, the last arsphenamin having been administered more than two months before. None of these patient had had any appreciable reaction.

The woman, twenty minutes later, became so dizzy that when changing cars she had to lean against a building. A little later, while on the car, she became very sick, and she vomited as soon as she reached home. Vomiting continued to be severe all night, and off and on the next day. As soon as the patient reached home, she developed a terrible, throbbing headache, which lasted for three days, and she could not raise her head. A one-fourth grain (0.016 gm.) morphin tablet, administered the first evening, did not relieve her at all. She began to have a severe chill one-half hour after reaching home, and for an hour or two her teeth chattered so that she could not talk, and her feet were cold. Two and three quarter days after the injection, she developed a severe herpes facialis, mostly on the chin, one patch being about 2 by 1¾ inches (5 by 4.3 cm.); and there was a small area on one finger. These became purulent later and her chin swelled greatly, 1 inch (2.5 cm.), her husband said, from the level of the mouth down. She gradually felt better after three days, but was very weak and remained in bed six days. I saw her for the first time, April 20, as other relatives were in the house, and she was afraid of their learning about the trouble. My name had been used so that she could not even have me come in as a consultant.

The husband, who received 0.5 gm. in the evening, had severe nausea within an hour, lasting all the next day, but vomited only twice. He had a severe chill three hours after treatment, lasting one hour and shaking the bed by its severity. A throbbing headache began two hours after treatment, lasting one hour. The patient was unable to work for two days.

The third patient had severe chills and nausea and vomiting that night, but felt well the next evening, so I gave him another injection. He had the same experience after this, but as he felt well the next evening I gave him a third injection. This did not affect him at all.

I have gone over every possible source with my nurse and the only difference from the regular routine was that I used new rubber tubing. In giving the third dose to the man, after which there was no reaction, I went back to the old rubber tubing. I have communicated with the firm from whom I bought the tubing, and they said it was a pure gum rubber tubing, bought from the same manufacturer for twenty years. Dr. Stokes reported in April, 1920, that they had between twenty and thirty cases of similar reaction after the use of new rubber tubing, but that soaking and rinsing the new tubing in normal sodium hydroxid solution for six hours removed the poisonous material.

Dr. Udo J. Wile, Ann Arbor, Mich.: I should like to express my appreciation of these papers. I have had a rather large experience with arsphenamin dermatitis and have repeatedly consulted with Dr. Schamberg regarding its possible cause. I have also discussed with Dr. Stokes the question of focal infection. In my particular type of material, the feature of focal infection is extremely hard to estimate, because almost all of our patients have some

type of focal infection. They come from a poor class of people, and all of them have infected teeth, if no other forms of infection. I have had an unusual opportunity to follow to postmortem two cases of arsphenamin dermatitis. In both instances, the patients were suffering with severe hepatitis, in one approaching acute yellow atrophy; and in one case our pathologist recovered almost 2 grains (0.13 gm.) of arsenic from the liver, making it very plain and sure that the ultimate damage could be ascribed to the damage to the liver. In my group of cases, neo-arsphenamin has been more frequently the cause of dermatitis than arsphenamin. In that respect, I think my experience is a little different from that of the others, including Dr. Stokes.

I have also been impressed with another factor: We go along for eighteen months or two years without any trouble, and then, within a month or six weeks, two or more cases will appear; and I have not been able to free myself of the idea that something in the drug at that particular time may have been the factor.

Regarding Dr. Dennie's paper, I was able to use the hyposulphite injections and was quite struck with the promptness with which the patients recovered. But I agree with Dr. Schamberg that, if the trouble has persisted for some time, it is difficult to see how they could be helped, and particularly do I fail to see how it could protect them against future damage. I have felt that once a patient develops an arsphenamin dermatitis, it is always dangerous to give subsequent treatment.

Dr. Harold N. Cole, Cleveland: We have recently had the unfortunate experience in our state of obtaining quite severe reactions from a batch of neo-arsphenamin from the Metz Laboratories, which was furnished to our hospital by the state department of health. There were three cases of severe collapse which followed the administration of the drug, also one case with severe gastric symptoms and one case of dermatitis exfoliativa. We understand that some of the same batch was furnished to two other clinics in the state, at the same time, with very severe reactions resulting. I question very much whether this can be laid to focal infections. Dr. Roth has recently done some interesting work in regard to the age of preparations of neo-arsphenamin and in regard to the temperature at which they are kept stored. He has found in his work done at the U. S. Public Health laboratory at Washington that neo-arsphenamin deteriorates quite decidedly after a period of six months, so that preparations which were formerly nontoxic may even become quite toxic. Because of this, we believe that it would be a good plan if the date of manufacture could be stamped on each tube of neo-arsphenamin that is placed on the market. Age apparently had no effect on the old arsphenamin, at least in Dr. Roth's experience. He also found that neo-arsphenamin kept at room temperature or at high temperature likewise deteriorates rapidly, and has suggested that it be kept on ice. In our estimation, every possible measure must be used to prevent the reactions and severe after-effects which are seen from time to time in the use of arsenical preparations.

Dr. Marcus Haase, Memphis, Tenn.: I wonder if you would care for the negative side of this question? Our service gives a minimum of 100 doses of arsphenamin a week; 80 per cent. of the patient are negroes. Since Sept. 1, 1919, we have given over 4,000 doses annually, and we have had no arsphenamin dermatitis. I say Sept. 1, 1919, because previous to that time, the patients were hospitalized, as Dr. Stokes' patients are at present. Our patients are treated in the clinic. The arsphenamin is given and they are permitted to go home in a short while, but they remain under the supervision

of a socal service worker. If the patients do not return within a week, the social service department is asked for a report as to the reason of nonattendance.

The usual dose in our service is 0.35 gm. This may seem a small dose, but many of the patients are quite young. The negroes in the South, as you know, are infected quite early. We have never deviated from our original technic of using water distilled on the day on which the treatment is given, and no solution is administered after an hour and a half after mixing.

Dr. Fred Wise, New York: I should like to confine my discussion to Dr. Gaskill's paper. The impression it gives is that procain may not be the factor in the production of some of these cases of dermatitis. That is an impression contrary to the one I have obtained in the last five years of practice. I think there is little question that procain and analogous proprietary preparations provoke dermatitis in susceptible people. It seems to me that the cases fall into two classes: one in which discontinuance of the drug results in almost immediate cure, and the other in which stopping the use of the drug has little beneficial effect.

Dr. Harry G. Irvine, Minneapolis: I should like to join Dr. Haase in presenting some evidence on the negative side of the arsphenamin dermatitis. We have always felt that some of the trouble was due to too little preliminary study and too large doses given at too frequent intervals. This has been disputed, but the fact remains that in our clinic, with a large number of injections, running from seventy-five to 100 doses a week, so far as I know only two cases of neo-arsphenamin or arsphenamin dermatitis have developed in that service. I think in both instances these were recurrent. The treatment was given when the patient had a history of dermatitis, and the history was not gone into carefully. We have been using the drug, practically always neo-arsphenamin, for ten years, and these are the only cases of arsphenamin dermatitis. We have had none of jaundice.

Dr. Walter J. Highman, New York: I think the great rarity of arsphenamin dermatitis is a positive indication that, in considering the subject, we are dealing with one that is peculiar much less to the drug than to the person who has the symptoms involved in the syndrome. I think that the trouble lies usually not in the drug or its administration, but in the susceptibility of the patient, and that, if the disease were due to the first two groups of causes there would be more cases than have been reported here among men giving arsphenamin or kindred preparations. Therefore, I think we must travel some of the subtle avenues that Dr. Stokes has traveled in his paper. What the definite thing is, is beyond our interpretation today, but that the thing is related to hypersusceptibility or susceptibility is probable. It is only a matter of dialectics whether the interpretation is anaphylaxis, allergy, idiosyncrasy or any of the time-honored terms used in relation to the phenomenon; but the fact remains that we must look in this more or less vague field for the cause of the phenomenon. I think the fact brought out by Dr. Stokes as to the smallness of the dose required in susceptible people to produce the phenomenon, and the fact that the reactions come very early indicate that they particularly affect only certain persons. I think, further, that in those cases in which the phenomenon has occurred Dr. Stokes probably gave the same solution to many other patients who did not respond pathologically. Therefore, I think it is along this line that the final interpretation will be made.

The same holds true in the group of cases that Dr. Gaskill reported. I have no doubt that procain causes dermatitis, and I have no doubt that many eruptions a dentist gets on his hands or body are today wrongly considered

as being due to procain, but I think there is no question that there is a definite affection so caused, and that this may be demonstrated by a percutaneous test. By the way, the reaction is not a wheal but a patch of dermatitis that develops within a few hours after the test is made.

Dr. William Allen Pusey, Chicago: I was interested in hearing Dr. Wise's view, and I think his is the only view we can accept. I am sure we have nonspecific sensitization and also that we must recognize specific sensitization. Certain factors stand out definitely in this form of dermatitis. First, it is not an arsphenamin dermatitis. It is a dermatitis produced by arsenic; you can get just the same forms of dermatitis from other forms of arsenic. I have seen just as severe a case of exfoliative dermatitis in a man who was given sodium cacodylate for psoriasis.

Now, it is also, I believe, beyond doubt that this accident occurs in people who have some sort of hypersensitization. That is shown by the fact that the dermatitis occurs early in the course of arsphenamin administration more frequently than after the long continued use of it. That does not demonstrate that the drug may not be at fault, because in giving the dose we employ we use a very large dose of arsenic, and if that is in a toxic form the preparation may be incriminated.

I wish to express my appreciation of the idea brought up by Dr. Dennie, and I do not believe anything should stand in the way of our accepting this on theoretical grounds. It is an interesting observation that these patients are discharged well ten days after an arsphenamin dermatitis, and I think we are greatly indebted to him for calling it to our attention.

Dr. Philip Kilroy, Springfield, Mass.: As to the possibility of a preexisting nephritis or hepatitis being responsible for the dermatitis, because lesions of the kidneys or liver have been found at necropsy, I wish to call attention to the fact that any metallic poison capable of producing a severe dermatitis must necessarily set up inflammatory conditions in the internal organs; that arsenic should limit its possibilities for ill to the skin would be improbable, and, in fact, a hepatitis is one of its admitted consequences. Consideration of the papers will, I think, convince us that the inflammations which follow the administration of arsphenamin preparations occur in people who have every known pathologic entity, as well as in the rara avis who is absolutely healthy; they have been recorded in those who have good teeth and bad teeth and false teeth, and in all of them we have to do with an inflammation of the skin due to arsenic poisoning, and in which personal predisposition is the main factor and a faulty preparation a bare possibility.

Dr. Carl Voegtlin, Washington, D. C.: I have been extremely interested in these papers because we have studied during the last three years at the U. S. Hygiene Laboratory the pharmacology of arsphenamin and its derivatives, and we have come to conclusions which seem to have a bearing on this question of arsphenamin dermatitis. First of all, we found that arsphenamin has certain peculiarities with regard to its pharmacologic action, on account of the fact that its fate in the body is subject to variations in different persons. If you inject a set of normal healthy rats of the same weight, the same sex and fed on the same diet, with the same lot of arsphenamin, you will find that some animals will die and some will survive, and this fact forced us to adopt for the official toxicity test the use of at least five rats. We furthermore found that arsphenamin, as such, is not directly toxic for the parasites in the tissues of the higher animals. These facts led us to the

conception that arsphenamin must first be metabolized in the body to an active modification ("arsenoxid") before it can exert its toxic and therapeutic action.

Now, naturally, if this is the case, we should expect to find all kinds of variations in pharmacologic action in different persons. We found, for example, that the rate of excretion of the arsenic of arsphenamin and allied arsenicals varies considerably in different persons. It appears to me, therefore, that the production of dermatitis in certain patients also depends on these variations in the fate of the drug in the body. Evidently, some members of your society look to the patient for an explanation of this toxic manifestation, rather than blame the quality of the drug used. To my mind, it would be remarkable, with the official toxicity control in effect, that just certain batches of the drug should produce dermatitis and not others.

Dr. Jay Frank Schamberg, Philadelphia: It is important in the interests of truth and of the safety of our patients that we do not prematurely commit ourselves to any definite view with regard to the cause of jaundice, dermatitis and similar complications. Within a few weeks, our research institute received from Dr. Stokes several tubes of arsphenamin from a lot which Dr. Stokes said had been producing dermatitis. He asked us whether we would not critically examine this lot with a view to throwing light on the origin of the trouble. The drug was retested in animals and passed the toxicity tests at the same high figure that it had previously done. It was then tested chemically to determine any evidence of oxidation. By all the tests at our command, there was no evidence of the increased formation of arsenoxid or any other oxidized product. Despite these negative results, I would not presume to state that the cause of the dermatitis was perhaps not resident in the drug.

Arsphenamin is so complex a compound that it is possible that some intramolecular change may have taken place which defies discovery in the present state of our knowledge. My feeling would be that any lot of arsphenamin from any laboratory in the world that gives an unusual incidence of reactions should be the subject of suspicion until other factors relating to the technic or to the patient had been discovered to be the cause of the same.

We are working for the truth, and the solution of problems of this kind should be settled on scientific grounds. With any suspicious lot giving rise to reactions, the laboratory issuing the drug should be notified of the lot number and a request made for a thorough reexamination of the product. It beclouds the issue invariably to excuse the drug and accuse the technic.

Dr. John H. Stokes, Rochester, Minn.: My experience has convinced me that the etiologic background of cutaneous reactions associated with arsphenamin therapy is exceedingly complex. While it would be comforting to be able to pin every such reaction on the drug, I believe that it is usually only one of a number of interacting factors. Exfoliative dermatitis is merely a symptom, as you well know. That it may follow the administration of mercury intramuscularly and of local irritants such as tincture of iodin has been exemplified in my own experience. It is the patient who does the reacting, rather than the drug. In one, a focal infection may predispose. In another, some peculiar intramolecular change may occur in the drug after injection. Again there may be individual idiosyncrasies in the hepatic metabolizing of the preparation. There must undoubtedly exist differences in the way in which different persons meet a chemical situation which confronts them, precisely as in the formation of anaphylatoxin, etc. The drug as such should not therefore be rashly incriminated. I recall Milian's statement that he had

investigated a so-called "erythematogenic series" of neo-arsphenamin and had kept a number of the ampules for use at a later time. In his second test of the series, no reactions developed.

In the case of Dr. Irvine's experience, I might suggest that the practically exclusive use of neo-arsphenamin may explain the fact that his clinic sees practically no reactions. Our doses are large. Six-tenths gram of arsphenamin or 1 gm. of neo-arsphenamin is not at all uncommon. In fact, I have been impressed with the relative immunity from serious complications possessed by patients under extremely intensive treatment. Six-tenths gram of arsphenamin may be given twice a week with daily injections of mercuric succinimid and large doses of sodium iodid intravenously, without any sign of reaction.

I might suggest that acute yellow atrophy of the liver cannot be regarded as a demonstration that a patient has died of arsenic poisoning. It is worth while to recall the observation of Symmers on acute yellow atrophy occurring in epidemic form in New York. I have alluded in greater detail to this question in a publication on catarrhal jaundice as a complication in the treatment of syphilis. Only recently, a patient whom we had seen two years before and who had had some arsphenamin at that time returned home without any further treatment, and, within a few days after his return, developed a jaundice which terminated, within a very brief time, in death from acute yellow atrophy of the liver, although he had received no arsphenamin and no treatment for syphilis for two years.

I agree with Dr. Wile that exfoliative reactions occur in groups or waves. These individual waves often show marked clinical differences. For example, I had never seen diarrhea associated with exfoliative dermatitis until the winter of 1921-1922, when I had six cases in succession, whose features are discussed in this paper. While clinical analysis of these questions has its weak points, it does seem to me to have a chastening effect. It leads us to realize that the mechanism behind many seemingly simple protests on the part of the body may be very complex.

Dr. Charles C. Dennie, Kansas City, Mo.: I wish to say that Dr. Pusey's criticism is very good. The title should not have been arsphenamin dermatitis, but arsenic dermatitis. One case occurred after the use of sodium cacodylate and one after a mixture of solution of potassium arsenite (Fowler's solution) and arsphenamin. I have also seen it in a child who received nothing but solution of potassium arsenite. Most of these cases we have seen early, when the sodium thiosulphate has the most influence. It is natural to suppose that, if the patient with mercuric chlorid poisoning is not seen until late, this method or any other would do no good; but, if these patients are seen within from two to six hours after taking the mercuric chlorid, the result is gratifying. In the cases reported by Strathy, in which the reactions occurred forty-five days after the injection, it was not the arsenic alone that produced this condition. We do not claim that the dermatitis is due to the arsenic alone, but to arsenic plus other factors. One preparation of arsphenamin is as likely to be followed by arsenic reactions as is the other; but when we stop to think of the doses given by experienced men, we reach the conclusion that arsphenamin injections can be given with more safety than any other intravenous medication.

Regarding Dr. Wile's remark concerning the recurrence of arsenic dermatitis, we will say that in the three cases of arsphenamin dermatitis in which sodium thiosulphate was given, there was no recurrence; why, we do not know.

It may be that the arsphenamin did not act; perhaps it was neutralized by the sulphur as soon as it entered the blood stream. Dr. Cole made the statement that these reactions occur with the first arsenical treatment. I agree with Dr. Stokes that these cases have occurred early rather than late in the treatment of the disease. In the cases of delayed arsenical poisoning in which we know that certain organs are injured, the liver and especially the kidney, and in which arsenic has been found in the organs long afterward, it is likely that if the arsenic were eliminated the patient would have a better chance for his life.

A BRIEF FOR THE MORE ACCURATE CLASSIFICATION OF INDUSTRIAL SKIN DISEASE*

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At the St. Louis meeting, I suggested the term "dermatitis industrialis" as the name to be applied to the group of cases presenting lesions on the skin caused by or associated with various industrial conditions. In the discussion, it was suggested that this term be changed to "dermatosis industrialis," in order to include the conditions which are not usually included in the dermatitis group, such as acne, epithelioma, folliculitis, keloid, etc. The term "dermatosis industrialis" is the better name, I believe, and should be more generally adopted in the diagnosis of this group of skin conditions. At the present time, the cases are scattered about under such various headings as dermatitis, dermatitis venenata, occupational dermatitis, acne, folliculitis, keloid, eczema, trade eczema, bakers' eczema, butchers' eczema, etc.

Not only is it advisable to group these under such a term, but it also seems reasonable to adopt a scheme similar to the one used in the classification of heart diseases; in other words, to group these cases under the heading "dermatosis industrialis," and then add to this diagnosis the qualifying words signifying the type of eruption and the causative element, if known; for example, dermatosis industrialis (folliculitis, oil); or dermatosis industrialis (venenata, formaldehyd); or dermatosis industrialis (eczema, flour), etc. If the cause is not known, the occupation can be inserted in its place, thus: dermatosis industrialis (eczema, dyeworker). The advantages of grouping these cases in some such manner in our classifications of disease are worth bringing to the more general attention of the profession.

In the first place, the prevalence of cases presenting an eruption on the skin associated with various occupations is a strong argument for grouping these conditions into one class and under one name. A recent review of over 2,000 cases of dermatitis, dermatitis venenata and eczema has shown that 11 per cent. of the dermatitis and dermatitis venenata cases, and 3 per cent. of all cases admitted to the skin clinic were occupational in origin. These statistics do not include (1) many cases in which there is some doubt; (2) numerous cases in which there is no statement on the patient's record in regard to the origin of the disease, and (3) many cases of eczema of the hands in housewives. It seems reasonable to estimate that 5 per cent. of dermatologic

* From the Dermatological Department, Massachusetts General Hospital.

cases seen in a large city clinic are probably industrial cases. The figures given by other writers indicate an even larger percentage.

The difficulty in arriving at any true concept of its prevalence can be appreciated only by one who has searched case record after case record under the various usual diagnoses. The patients are seen in the clinic, examined, the condition diagnosed and treatment given; but for any study of a group of workers in a certain trade, or workers with an eruption from a certain substance used in various trades, there is no way of obtaining material except through the examination of a large number of records.

The importance of preventive measures in dealing with these conditions further necessitates the placing of these various skin conditions in a definite group. The workmen's compensation acts are focusing attention on these conditions, and the interests of both employer and employee demand a more accurate classification; for it is only in some such way that these cases may be brought together and carefully studied. Prevention is the important factor, and the need of attaining such a result furnishes a practical argument for the adoption and general use of some such term as "dermatosis industrialis."

These skin conditions are a distinct group by themselves. They are a group with a common etiologic factor: work done by the individual, or substances with which the workman comes in contact. It is true that the various individual causes are very numerous, both chemical and mechanical, and the condition is undoubtedly due to individual susceptibility on the part of the patient. It is logical, however, for classification and for study, to regard these cases as a separate disease. It also seems reasonable that the classification of this group of cases under one head will stimulate interest in occupational skin conditions and ultimately contribute much toward the prevention of these various conditions.

This group of cases can be compared to the group to which the name "dermatitis medicamentosa" is now given, the group in which the skin condition is due to a common etiologic factor: the absorption of some drug. The conditions in these two groups are similar. There are numerous factors in each group which may cause dermatologic manifestations, and these manifestations may present varying types of lesions. There are many different drugs which may cause an eruption on the body and there are various types of eruptions produced by drugs. The eruption may vary from erythema due to one drug, to folliculitis due to another, to purpura due to another, etc., or there may be at times a multiform eruption. The eruption associated with various industries varies in the same way: perhaps a real dermatitis venenata in one case, eczema in another, folliculitis in another, etc. The multipli-

city of trades and substances known to cause skin irritation is no bar to including these conditions in one group.

It is also a decided advantage to remove these conditions from the eczema group. The term "trade eczema" is one of long usage and has become a rather commonly accepted term in the persistent type of case; but it would be far better to separate this class of cases entirely from the diagnosis "eczema," grouping them under one heading which would ally them more intimately with their etiologic factor and at the same time include the other types of industrial dermatologic lesions. Numerous subtractions have been made from the group of eczemas in the past, and the use of this term presents the opportunity to split off another group from this already too large rubbish heap "eczema."

The term "dermatosis industrialis," while perhaps not a true Latin term, is at least latinized, and naturally will fit better into the various classifications of diseases in which the terms are all Latin or at least have Latin endings. The argument has been used that "dermatitis occupational" does not fit well in a classification between two distinctly Latin terms; whereas "dermatosis industrialis" will correspond with other terms such as "dermatitis herpetiformis" and "dermatitis medicamentosa" in the usual classification. In fact, such an argument has already been used when the attempt was made to have "dermatitis occupational" inserted in a hospital classification of disease.

It could perhaps be argued that certain cases of acne or folliculitis, or ulcers, etc., from industrial conditions, would be classed under the term "dermatosis industrialis," and would not appear in the statistics with these particular diseases. At the present time, in the average classification, these industrial cases are lost entirely for the study of industrial conditions and, therefore, shed no light on the prevention of these conditions. I believe that classification under one heading would serve a far more useful and practical purpose than classification under the particular manifestations of disease. However, in any good system of cross cataloging, an entry could very well be made on the proper card: acne, folliculitis, etc., as well as under the term proposed.

The same objection might be raised to "dermatitis medicamentosa" —that the bromid acne and the folliculitis from potassium iodid, etc., are lost for statistical purposes. Common usage has sanctioned the classification of these conditions under "dermatitis medicamentosa," and there is every reason to believe that this would in time be true of the present suggested term.

Let me reiterate the argument which I presented fiirst: the very prevalence of this condition, the frequency with which these cases are coming to our attention in clinics and in private practice (5 per cent.,

or probably more, of all our cases of skin disease), furnishes a potent argument for a generally acceptable plan for a more accurate classification of this increasingly important group of skin conditions.

SUMMARY

The adoption of the term "dermatosis industrialis" in the diagnosis of pathologic skin conditions from industrial causes is urged, to be employed in conjunction with two qualifying terms, one signifying the type of eruption and the other the causative element, if known, or the occupation if the exact cause is not known.

DERMATITIS VENENATA

A STUDY OF THE TROPICAL PLANTS PRODUCING DERMATITIS *

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Among the luxurious and rich tropical flora there are several plants, the latex, secretions or appendages of which are injurious to the human skin. These plants grow wild in the thick forests of the Antilles and in the country around the towns and cities. The well-known *Rhus toxicondendron* does not exist in the tropics, but there are other plants, such as the comocladias, that produce dermatitis very similar to if not identical with that produced by the ivy, and many others that produce skin reactions that vary from erythema and pruritus to acute vesicular dermatitis with severe general disturbance. These plants are little known to the medical profession, although their irritating and poisonous properties have been observed for many years. We have endeavored to make a preliminary study, from the botanical, physiologic and chemical point of view—not a complete and exhaustive study of these interesting plants and the clinical phenomena which they produce. Our aim is to make them known and awaken the interest of the chemist, principally, as undoubtedly the substance which is responsible for the skin manifestations has not been isolated.

The tropical plants that produce dermatitis are listed in the accompanying table.

ANACARDIACEAE

The most important of the anacardiaceae are the comocladias, and among them *Comocladia dentata* is typical. All the varieties are known under the common name guao and all have the same properties. In Cuba, *Comocladia dentata* is widely distributed. In Porto Rico, it is called carasco and, in the British Antilles, tooth-leaved maiden plum. *Comocladia dentata* is from 3 to 6 feet (0.9 to 1.8 meters) high; in the wild forests, it may reach 12 feet (3.6 meters). It has a slender brown trunk, with many branches. The leaves are oblong and pointed, alternately situated, dark green, and hairy on the inferior surface. These hairs are straight or curved and conic-shaped, containing four cells and covered with a thick membrane. The leaves of many other varieties of the comocladia are hairless. The edges of the leaves are provided with from eight to twenty thornlike prominences, corresponding to the endings of the bifurcations of the central nerve. The flowers are small

* Read at the Forty-Fifth Annual Meeting of the American Dermatological Association, Washington, D. C., May 2-4, 1922.

and dark purple, growing in clusters. The latex, which is found in moderate quantities in all parts of the plant, and very abundantly in the green boughs and leaves, is a heavy yellowish-white fluid, which turns black under the action of light. This latex is highly irritating

TROPICAL PLANTS PRODUCING DERMATITIS

Genus	Species	Common Name
Anacardiaceae	Comocladia dentata, Jacquin	Guao
	Comocladia glabra, Sprengel, variety acuminata	Guao
	Comocladia hollikii, Britton	Guao
	Comocladia grandidentata, Britton	Guao
	Comocladia Ehrenbergii, Engler	Guao
	Comocladia parvifolia, Britton	Guao
	Comocladia cordata, Britton	Guao
	Comocladia pubescens, Engler	Guao
	Comocladia jamaicencis, Britton	Guao
	Comocladia velutina, Britton	Guao
	Comocladia pilosa, Britton	Guao
	Comocladia ondulata, Urban	Guao
	Comocladia intermedia, Wright	Guao
	Comocladia platyphilla, Richard	Guao
	Comocladia dominguensis, Britton	Guao
	Comocladia dodonaeae, Britton	Guao
	Comocladia acuminata, Britton	Guao
	Metopium browneii, Urban, or M. toxiferum, Linné	Guao de costa
	Anacardium occidentale, Linné	Marañón
	Rhus venosa, Grisebach	
	Rhus metopium, Linné	
Leguminosae	Mucuna pruriens, DeCandolle, or Dolichos pruriens, Linné, or Stizolobium pruriens, Medicus	Pica-pica, cowhage, cowitch
Euphorbiaceae	Platygyne pruriens, Baillon, or Platygyne urens, Linné	Pringamoza
	Tragia volubilis, Linné	Pringamoza morada
	Jatropha urens, Linné	Chaya
	Hura crepitans, Linné	Salvadera
	Euphorbia lactea, Haworth	Cardon
	Jatropha curcas, Linné	Piñón de botija
	Hippomane mancinella, Linné	Manzanillo
	Acidoton urens, Sw. E	
	Acidoton microphyllus, Urban	
Urticaeae	Fleurya umbellata, Weddell	Ortiguilla
	Fleurya aestuans, Gaudichard-Beupré	
	Urera baccifera, Gaudichard-Beaupré	Chichicate
	Urera dominguensis, Urban	
Malpighiaceae	Malpighia urens, Linné	
Malvaceae	Malachra urens, Poiteau	Malva Santo Domingo
Lytrareae	Cuphea urens, Kaehne	
Araceae	Phylodendrum consanguineum, Schott	
Apocinaceae	Tabernaemontana citrifolia, Linné	Pegojo

and is the cause of the skin lesions which we shall describe. *Metopium toxiferum* is found near the coast, which accounts for its common name, shore guao. This variety is supposedly more dangerous, and the country folk are particularly careful to avoid it.

Clinical Lesions.—It is a common belief that the shadow of the comocladias produces swelling and inflammation of the skin. As is the case with other poisonous plants, this has been attributed to some volatile substance escaping from the plant. The fact is that sensitive persons are rapidly affected on coming near the plant and others are affected on coming in contact with its leaves or bark. Many people, regardless of race or age, are immune to the injurious substance in these plants. I have handled the leaves and the bark without ill effect, but a drop of the sap deposited on the skin of the wrist produced a lesion similar to a second degree burn, which lasted for many days. Sensitive persons are affected when merely passing near or on approaching a grove of comocladias. Colored people are as sensitive as white. The eruption is polymorphous, appearing preferably on the face and arms. In males, the scrotum is also a site of predilection. The first phenomena are those of intense pruritus and edema; the eyelids appear puffed to an extent that makes their opening impossible; the lips are swollen, and through the open mouth the saliva dribbles; the ears appear twice their size, and the hands, and especially the scrotum, are tremendously edematous. The patient presents at first sight a weird and indescribable picture. The redness soon appears in blotches with the formation of wheals, papules, vesicles and bullae. The vesicles and blisters may appear directly on the apparently sound skin, owing to the lifting of the epidermis in toto by the sudden and pressing edema, or may form on top of a wheal or papule. They are filled with clear serous fluid, and sometimes become purulent through secondary infection. At this period, the patient presents an appearance similar to that of a patient suffering from a severe case of poison ivy. The vesicles discharge for a week or ten days, the edema and inflammation gradually subside, and the case ends with abundant lamellar desquamation. In severe cases, there is considerable pigmentation, which may last for a long time.

The subjective phenomena are those of intense pruritus and burning sensations. Pain may be felt in cases in which the bullaes are very large and their breaking leaves the epidermis unprotected. In these cases, the lesions are very similar to second degree burns. The disease leaves no trace but pigmentation, except in case of secondary infection, when ulceration and subsequent scarring may occur. The general disturbance is slight or nil in mild cases; in severe cases the temperature may be as high as 40 C. (104 F.), and the itching, sleeplessness and nervous condition of the patient combine to make his condition very wretched. There may be a transient albuminuria. One attack confers no immunity. The peasants believe that eating the fruit of these plants makes them immune to further dermatitis, and a colored boy assured me that he was a constant victim of dermatitis until he ate the seeds of the ripe fruit. This boy helped our party to gather leaves and bark from the

tree without ill effects. In this connection, it is well to remember the successful experiments of Strickler and Schamberg on the desensitization of susceptible persons by intramuscular injection and internal administration of poison ivy.

Chemical Investigations.—The latex of *Comocladia dentata* contains an enormous amount of tannin. The active principle seems to be an essential oil, which may be recovered in small quantities by distilling the alcohol from the macerated bark and leaves. This essential oil is light brown and has a peculiar pungent odor. When applied to the skin, it produces marked irritation.

LEGUMINOSAE

Mucuna Pruriens.—This climbing vine, commonly known in Cuba as pica-pica and in the English speaking communities as cowitch or cowhage, is quite abundant in all parts of the Antilles. There are two varieties, *M. altissima* and *M. urens.* Its leaves are in branches of three, oval and hairless. The fruit is a pod from 3 to 6 inches (7.5 to 15 cm.) long and about 1 inch (2.5 cm.) wide, containing six or eight seeds, smooth and dark. It is covered with innumerable reddish hairs, which give it a velvety appearance. These hairs come off very easily and, transported by the wind, may affect the passerby, producing severe skin reactions. The hairs of the mucuna are conical in shape, pointed and straight, although they are sometimes slightly curved at the end. They are covered by a yellowish membrane, which is provided with small hooks turned toward the base of the hair. Microscopically the hairs appear divided into small cells containing droplets of an oily substance.

Chemical Investigations: The covering membrane shows the typical reactions of cellulose. With litmus paper, with phenolphthalein in solution and with aqueous solution of litmus, the hairs showed no reaction. On the other hand, there was marked acid reaction when they were soaked in alcohol and ether, which shows that the active substance is soluble in these liquids and insoluble in water. The reagents of Bouchardat, Sonneschein, Mandelin, Fröhde, Elias, Tanret and Dragendorff gave negative results, showing the absence of alkaloids. The oily substance that is found in the hairs is slightly yellow. It stains red when treated with sudan III, red brown with tincture of alkana and black with osmic acid. The oil is not attacked by hydrochloric acid. It is insoluble in xylene and purified petroleum benzine and soluble in alcohol, sulphuric ether, benzin, acetone, carbon sulphid and chloroform. It is not attacked by caustic potash, 10 per cent.

The oil of mucuna is a fatty acid oil, being probably a mixture of several fatty acids. When dry, it forms a resinous substance, orange in color.

Clinical Lesions: On coming in contact with the skin, the hairs of *Mucuna pruriens* immediately produce intolerable itching. If the patient refrains from scratching, there develops, at the end of five or ten minutes, an erythema and small punctate papules of edematous character. If the skin is moist with perspiration, the itching is more severe. In the majority of cases, these pure lesions are combined with scratch marks and the swelling and inflammation produced by the traumatism caused by the nails. The condition is usually localized, the uncovered parts being naturally most affected, but occasionally more extensive cases are seen, especially in country workers during the clearing of the fields for sugar cane plantations. In these cases, the unfortunate laborer may get in the thick of the vine, and be virtually covered with its hairs. With the hand lens, the small pointed hairs may be seen sticking into the epidermis, and around each one there appears a wheal of variable size. The mode of action of these hairs has been thought to be only mechanical, but the presence of the irritating oil in their cells proves that, although mechanical irritation may play a part in the symptoms observed, the chemical action of the oil is really responsible for the condition.

The peasants rub on dry ashes to allay the itching, and any alkaline application, in fact, will relieve the condition. The eruption lasts for several hours, then disappears, leaving no trace.

EUPHORBIACEAE

Practically every euphorbiaceae contains a caustic substance which produces an acute dermatitis when the sap is applied to the skin. We shall pay no attention to those that need to be applied on purpose to produce their effects, such as *Euphorbia lactea, Croton liglium* and *Jatropha curcas.* Those that accidentally or by the slightest contact produce skin reactions may be divided into two groups: those that act through the irritation produced by their appendages, generally prickles or hairs, and those the latex of which contain a highly irritating substance. Among the first group, we shall study *Platygyne pruriens, Tragia volubilis* and *Jatropha urens;* among the second, *Hippomane mancinella* and *Hura crepitans.*

Platygyne Pruriens and Tragia Volubilis.—The first is known under the vulgar name of pringamoza and the second as pringamoza morada. In Jamaica, both are called twining tragia. Both species are wild vines, growing profusely in the forests. The leaves are opposite, oblong in shape, of dentated edge and studded with innumerable cone-shaped silvery hairs. The fruits are small, dehiscent capsules, with four or six seeds arranged in pairs and placed in axillary bunches. The flowers are purple in *Tragia volubilis* and lighter in *Platygyne pruriens.*

The fruits are also covered with very stiff hairs. These hairs are the irritating parts of the plant. Under the microscope, they appear straight or slightly curved. Those from the skin of the fruit are brown and highly refractile; those from the leaves are lighter, being nearly white, and transparent. They are provided with a thin membrane and contain a long, oblong or triangular cavity filled with two or more droplets of an oily substance. The point of the hairs seems to be very resistant, forming in the longer and larger hairs a sort of solid spicule. The surface is smooth, but, occasionally, small globular thickenings are seen.

Chemical Investigations: The chemical study was conducted along the same lines as in the case of the Mucuna pruriens. The oily sub-

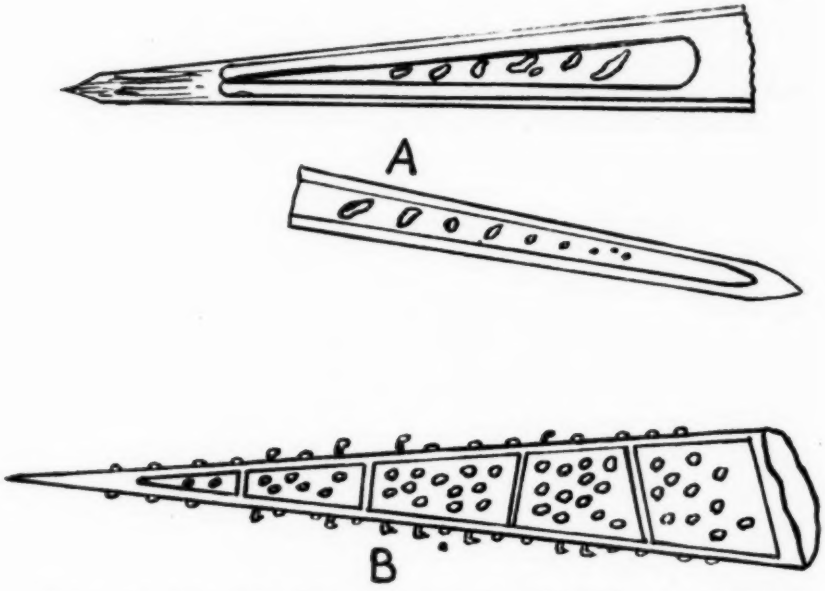

Fig. 1.—*A*, hair of Platygyne pruriens; *B*, hair of Mucuna pruriens.

stance in the hairs gave a marked acid reaction when dissolved in alcohol or ether. The tests for alkaloids were all negative.

Clinical Symptoms: The prickles, on the slightest contact, produce severe itching, erythema and urticaria. Foresters and hunters suffer severely, as the worst case of urticaria toxica cannot be compared with a common case of this dermatitis. The exposed parts are mostly affected; but the prickles are so numerous and cling to the skin with such tenacity that generalized eruptions are not infrequent. Moisture from perspiration increases the itching. Alkaline applications and hot baths afford relief. The eruption lasts a few hours and leaves no trace.

Jatropha Urens.—The vulgar names of this plant are chaya and stinging physic nut. The jatropha is a small tree, from 4 to 6 feet (1.2 to 1.8 meters) tall, very common in the Antilles, Guianas and Venezuela. There is a cultivated inermes variety, which is harmless. The plant branches out profusely 1 or 2 feet from the ground; its leaves are wide, three lobulated and alternate. The flowers are yellow or red, in axillary or terminal clusters. The fruit is a capsule. The leaves and their pecioli are covered with white stiff hairs, very sharp and resistant, which contain an irritating substance. These hairs are obliquely implanted and measure as much as 1 mm. in length. Under the microscope, they appear light colored and are surrounded

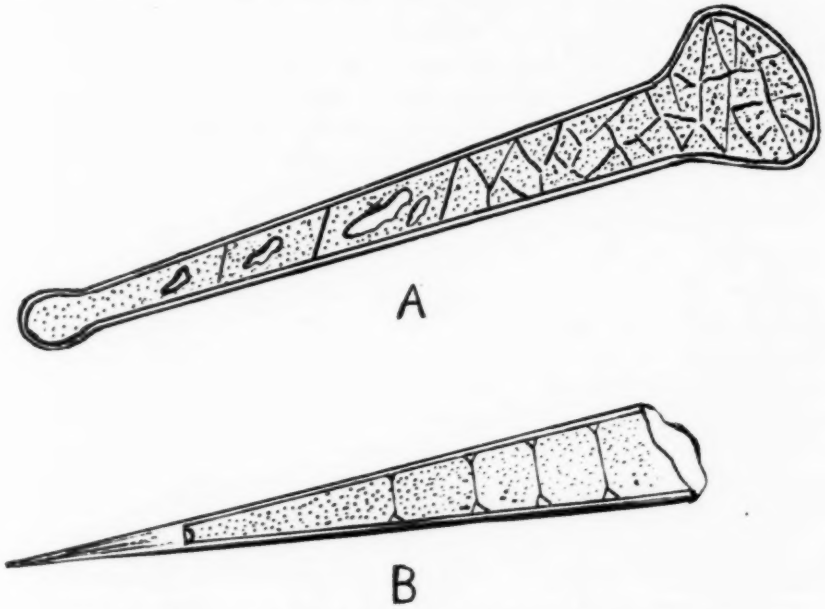

Fig. 2.—*A*, hair of Jatropha urens; *B*, hair of Fleurya cuneata.

by a double membrane which encloses an oval or triangular cavity divided into variously shaped cells by numerous intervening thin partitions. These cells contain a granular substance and also droplets of a highly refringent oily substance. The end of the prickle is not pointed as in the pringamozas and the mucuna, but is round and club-shaped.

Clinical Symptoms: The leaves of this plant, when rubbed on my forearm, immediately produced intense burning and smarting. With the hand lens, it could be observed that the sharp hairs had penetrated the epidermis and were firmly imbedded. At the points at which the hairs had pierced the skin, there were small purpuric spots, around which there developed in a short time raised, firm wheals of variable

size, the largest being about one half inch in diameter. The burning sensation—there was really no itching—continued for several hours, the lesions finally disappearing; but the purpuric spots lasted for several days, with a sense of discomfort when the parts were lightly rubbed. I had occasion to observe three members of one family suffering from the same condition. A visit to their garden revealed the existence of two specimens of *Jatropha urens,* of the irritating properties of which they were ignorant.

Chemical Investigations: The oil contained in the hairs of this plant is the irritating material that produces the clinical lesions described. It seems to be an oil with the characteristics of that of the pringamozas. Chemical investigations are quite difficult to carry out, as it is nearly impossible to collect enough material for study.

Hippomane Mancinella.—The vulgar names of this plant are Manzanillo and common manchineel. This is a handsome tree of dense foliage; the leaves are alternate and accuminate, with two small glands at the base. The fruit is a drupa similar to a small apple, with six seeds.

This plant has been known for years in Cuba as the most poisonous plant of the Antilles. It is a common belief that its shadow produces swelling and fever, and that the seeds when eaten by fish render the latter highly poisonous. The Indians used the sap of this plant to poison their arrows. Some animals, such as cows, horses and certain fowl, eat the leaves without any ill effects, apparently.

Clinical Symptoms: The latex obtained by incisions in the bark of the tree is a milky-white thick fluid which solidifies after a time. A drop of it placed in a wound on the foot of a rabbit or a guinea-pig kills the animal in a few minutes. Some cases of poisoning, accidental or criminal, have been reported, with the following symptoms: burning sensation of the alimentary canal, diarrhea, vomiting, cramps, profuse perspiration, dyspnea, coma and death. On the skin, the reaction produced varies with different persons, from simple erythema and pruritus to vesicular and bullous eruption with serious general symptoms. Some investigators have denied the caustic action of the sap of this plant on the skin, but I have seen and personally experienced the irritating properties of it. Personal susceptibility is to be considered, some persons being practically immune and others highly sensitive.

Chemical Investigations: The latex of *Hippomane mancinella* is a white creamy fluid, which solidifies after a time and becomes brown. When fresh, it is very caustic, and a drop on the skin raises a large, inflammatory vesicle in a short time. It gives a marked acid reaction with litmus and phenolphthalein. It is slightly soluble in hot water and soluble in alcohol in all proportions. Treated with the reagents of Bouchardat, Mandelin, Fröhde, Elias, Tanret and Dragen-

dorff, there is no indication of the presence of alkaloids. The aqueous solution, acidified wth hydrochloric acid and heated, reduces the copper of the Fehling solution. The aqueous solution decolorizes a 1 per cent. alkaline solution of safranin.

These last two mentioned reactions point to the existence of a glucosidal substance. This glucosid was isolated in the following manner after the method recommended by Dr. Fernandez Benitez:[1] Ten grams of the dried latex were dissolved in 120 c.c. of water and 20 c.c. of pure alcohol and boiled for two hours, the liquid lost by evaporation being replaced. After cooling, a concentrated solution of lead subacetate was added, which produced a heavy white precipitate. This precipitate was separated by filtration. The remaining liquid was treated with hydrogen sulphid to remove the lead, and then evaporated to a fifth of its former volume, the evaporation being allowed to finish at room temperature. The residue obtained was an amorphous yellowish-white powder, slightly soluble in cold water and readily soluble in hot water. The solutions of this powder acidified with hydrochloric acid, reduced the copper of the Fehling soluton and gave the characteristic dark blue when heated with Cotton's reagent at 75 C. This glucosidal substance isolated from the sap of *Hippomane macinella* seems to be the active poisonous substance in this plant.

Hura Crepitans.—This tall and handsome tree is commonly known as salvadera. It is seldom seen near the cities, where it is little known. The leaves of this tree are wide and oval and hairless. They are provided with two small glands at the base. The fruit is a dehiscent capsule. The sap produces a marked erythema and intense itching; this erythema sometimes resembles erysipelas. The caustic properties of the latex of this plant are due to a crystaloid substance isolated by the French botanist M. Bossingault, who named it hurin. Hurin is soluble in ether and alcohol and insoluble in water. It melts at a temperature of 100 C. and is decomposed at higher temperatures.

Other Euphorbiaceae.—The Euphorbia lactea is used on many farms for hedges. It contains a great amount of white latex, which may produce a severe conjunctivitis. On the skin, it acts as a rubefacient, and in some people it may produce an erythematous and vesicular dermatitis when rubbed in. *Jatropha curcas,* vulgarly known as piñon de botija, may produce skin reactions, but they are never severe or serious and seldom require medical attention. The fruit of this tree contains a substance which is highly poisonous. I saw two small children who had partaken of these fruits die in three hours, with all the symptoms of acute poisoning by strychnin or curare.

1. Fernandez Benitez, J. A.: Estudio Fisiologico, Quimico y Toxicológico del Arbol del Manzanillo, Rev. Med. Cir. Havana **12**:247 (June 25) 1908.

URTICACEAE

Fleurya Umbellata.—The vulgar name of this plant is ortiguilla. This is a small herb, scarcely a foot high, of fibrous cortex, covered with white pointed hairs. The leaves are simple, alternate, dentated and also covered with numerous hairs. The flowers are small and white, and in axillary clusters.

The hairs are silvery white, and from 1 to 2 mm. in length. Microscopically, they appear conical in shape and divided into four or five compartments containing a granular substance.

The skin disturbance caused by the hairs of this plant is a maculopapular dermatitis, very pruriginous and usually limited to the exposed parts. As the plant grows wild in the fields, forming patches among other grasses, it is not uncommon to see those who go barefooted suffer a severe dermatitis that reaches up to the middle of the leg.

SUMMARY AND CONCLUSIONS

1. There are more than forty species of plants in the Antilles that produce skin reactions, varying from erythema and pruritus to severe bullous dermatitis, with serious general disturbance.

2. These dermatitides are produced by the latex of the plants or by their appendages, generally the hairs. The latex of *Comocladia dentata* contains a very irritant oil. A substance of glucosidal nature has been isolated from *Hippomane mancinella*. The hairs of the other plants studied act not only mechanically but also chemically, owing to the existence of an irritating acid oil.

3. The ingestion of certain parts of the plant—the fruit in the case of *Comocladia dentata*—seems to produce immunity.

4. The hairs of the different plants studied have differential characteristics which may prove of importance for the diagnosis of the offending plant, especially in cases in which the cutaneous reaction is so similar that, unless the hairs found on the skin are examined, the diagnosis is impossible.

LACQUER DERMATITIS

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July 13, 1920, M. K. B., a man, aged 32, came to me, with a dermatitis of his forearms and hands. It was a rather acute papulovesicular dermatitis which suggested external irritants as its origin. He had spent a day in the woods the week before, and the dermatitis had come on soon afterward. I concluded it was a dermatitis due to contact with irritating plants, probably poison ivy. I treated him with wet dressings of aluminum acetate solution, and he soon recovered.

The same patient came to me again, July 6, of this year. He had a papulovesicular dermatitis of his forearms and hands, acute, but not intense, consisting for the most part of discrete inflammatory lesions. This time there was no history of contact with vegetation that might have caused the trouble. There seemed to be no doubt, however, that it was an external irritant dermatitis, and I turned him over to my assistant, Dr. L. F. Weber, and asked him to find the irritant. He came back with a report that it was a Japanese lacquer dermatitis. The man was a dealer in cheap novelties, such as pedlers sell on the streets at holiday times. On the Fourth of July, his business is the selling of small canes which are used for carrying flags and pennants. This attack had come on just after he had been handling these canes for the Fourth of July, and Dr. Weber had worked out the apparent causal relation between handling the canes and the attack of dermatitis.

He brought one of the canes to the office. Dr. Weber made an alcoholic solution of the cane's varnish and made cutaneous tests. The tests made with the alcoholic extract of the lacquer showed a large inflammatory wheal the size of a ten-cent piece, which appeared in about four minutes, and had not begun to subside in three quarters of an hour. There was no reaction in the control tests made with the same alcohol without lacquer. There was no itching in the two control tests, while in the lacquer test the itching was intense.

The same cutaneous test with the alcoholic solution of the lacquer was made as a control in six other persons. In no case was any reaction produced.

Lacquer is made from the Japanese lacquer tree (*Rhus vernicifera*), and according to Toyama it has been recognized in Japan and China as the cause of dermatitis for more than a thousand years. It is, of course, known among us as a cause of dermatitis, but my impression

is that it is recognized as such with great rarity. I have never had a recognized case before in my experience, and there are few references to it in dermatologic literature.

Buraczynski [1] has reported a case in a gardener in Vienna which came on quickly after transplanting some plants of *Rhus vernicifera*

Rost [2] has reported cases.

Toyama,[3] in a paper on rhus dermatitis, describes the condition as it occurs in Japan.

I have found no report of the affection in American and British literature. The explanation is probably that the condition is overlooked. I failed to find it in my case, and I believe its discovery by Dr. Weber in a subsequent attack in my case was a clever piece of work.

The irritant substance seems to be remarkably stable. Dermatitis is produced not only by contact with the fresh plant, but also by contact with old varnish. Toyama says that he and his associates proved by experiment that lacquer taken from an antique jar which had been buried in a Japanese ruin for about a thousand years contained the irritant. He concludes, therefore, that it is manifestly not a volatile poison.

The two attacks that I have seen do not differ symptomatically from mild attacks of dermatitis due to *Rhus toxicondendron* or *Primula obconica*. These attacks yielded rapidly to wet dressings of aluminum acetate solution, as do poison ivy and primrose dermatitis.

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1. Buraczynski: Wien klin. Rundschau, No. 50, p. 955; abstr. Brit. J. Dermat. **15**:190, 1903.

2. Rost: Wien. med. Wchnschr. **27**:101, 1914.

3. Toyama: J. Cutan. Dis. **36**:157, 1918.

THE RESISTANCE OF HAIR TO CERTAIN SUPPOSED GROWTH STIMULANTS*

MILDRED TROTTER
ST. LOUIS

There is a popular belief, apparently shared by not a few physicians, that the amount of hair growth is readily influenced by external factors. For example, it is commonly supposed that cutting the hair makes it grow better, that cold cream is likely to cause an excess development of hair, and that sunburn and tan are also very favorable to hair growth. It is difficult to find in the literature records of definitely controlled data either in support or in refutation of such views. This study was undertaken for the purpose of testing the validity of some of these current ideas.

Suitable material for such tests must necessarily be living persons, and I am greatly indebted to several friends who willingly acted as subjects and thus made the study possible.

NORMAL RATE OF GROWTH

It was necessary at the start to have some information as to the normal character and rate of growth of hair in the different regions to be studied. Ten subjects, eight women and two men, afforded data for these preliminary observations. Four regions were considered: the axilla, a spot on the head just back of the vertex, the outer side of the forearm, and a region on the leg just below the knee. These selected areas were shaved very closely, and then at weekly intervals several hairs were pulled out by means of eyebrow tweezers, placed in small envelops, and later measured. The differences between the successive measurements, after the first seven-day period, showed the weekly rate of growth. The measurements included the root, the length of the shaft under the skin, and the length which the shaft had grown since the close shaving. The first week's measurements could not be used because the part of the hair shaft which is embedded in the skin cannot be readily determined after the hair is pulled out. Assuming that the length of the root and that part of the shaft under the skin is approximately constant, the difference between the first and second measurement gives the length which the hair had grown during the first period of seven days. For each measurement the average of

*From the Department of Anatomy, Washington University School of Medicine.

*This investigation was made in connection with work supported by a fund given to the Washington University School of Medicine for use in the study of hair.

from three to six hairs was taken. There was a slight individual variation in the rate of growth but no indication that it was correlated with age, sex or the color of the hair. This question, however, needs more careful investigation. The accompanying table summarizes the results for the different regions, showing the average measurements in millimeters for all persons.

The regions are listed in the order of decreasing diameter of the hair which covers them; that is, the hair in the axilla has the greatest diameter, the hair on the head has the next greatest diameter, and so on. The average weekly rate of growth, shown in the last line, decreases in the same order and seems to indicate a correlation with the diameter of the hair.

The danger of error in these observations lay not so much in the measuring as in the selecting of typical hairs at the weekly intervals. There was a possibility of getting the successor of a hair that had fallen out before the experiment was started, or one that had reached its

MEASUREMENT OF HAIR FROM DIFFERENT REGIONS IN MILLIMETERS

	Region							
	Axilla		Head		Leg		Arm	
Week	Length	Growth	Length	Growth	Length	Growth	Length	Growth
First	6.6	....	6.0	....	5.0	....	4.0	....
Second	9.6	3.0	9.0	3.0	7.2	2.2	5.5	1.5
Third	12.0	2.4	11.8	2.8	9.0	1.8	8.0	2.5
Fourth	15.6	3.6	14.4	2.6	11.4	2.4	10.0	2.0
Fifth	18.2	2.6	16.9	2.5	12.8	1.4	11.2	1.2
Sixth	21.0	2.8	20.4	3.5	13.5	0.7	12.4	1.2
Seventh	23.6	2.6	23.3	2.9	14.8	1.3	13.2	0.8
Eighth	27.5	3.9	26.8	3.5	16.0	1.2	....	....
Ninth	30.0	2.5	27.9	1.1	17.2	1.2	....	....
Tenth	....	....	29.8	1.9	19.0	1.8	....	....
Eleventh	....	....	33.3	3.5	21.2	2.2	....	....
Weekly average	....	2.92	....	2.73	....	1.62	....	1.52

ultimate length. This was guarded against as much as possible by using the average measurements of several hairs, rather than depending on one as a typical representative of the whole region.

In one case several hairs on the arm and leg were measured in situ and then marked so that identification for subsequent measurements would be certain. On the arm the area around the hair was stained with fine dots of gentian violet. This method is not very satisfactory, in that the stain washes off easily and must therefore be renewed daily. On the leg the hair was marked by injecting a small amount of gentian violet under the skin and close to the hair with a hypodermic needle. The needle was slanted away from the hair so that the injection could in no way affect the root. Measurements of the identified hairs were almost similar to those made in the other manner and, since the former method was less inconvenient to the subject, it was used.

Of these individually identified hairs, some reached their ultimate length during the experiment. Several of them attained it as much as

eleven weeks before the experiment was concluded, and at the end of the experiment they were still intact. This makes it appear that a hair on the arm or leg does not fall out and is not replaced by a new one for something more than eleven weeks.

EFFECT OF PETROLATUM

Petrolatum ranks very high in the popular estimation as a stimulant of hair growth. It is, therefore, frequently used on the eyebrows, but is seldom, when used by women, allowed to touch the face. Bilaterally symmetrical regions were selected for the purpose of testing the effect of this substance on normal hair. The two sides were carefully compared to insure that they were similar, treatment was begun on one side, and the other side was used as a control. Four women, between the ages of 22 and 26, took part in this experiment. Three of the subjects applied petrolatum to the front of the right thigh twice a week for a period of eight months. The other subject applied it to the right eyebrow approximately twice a week for four months. In each case, a generous supply of petrolatum was rubbed on thoroughly, but not vigorously enough to cause reddening or hyperemia of the skin. The aim was to give the petrolatum ample opportunity to show its own effect without introducing any complication due to massage. At the end of the period the two symmetrical regions in each subject were compared very carefully by three observers and absolutely no difference was detected. Two of the observers were necessarily unbiased, for although they knew the nature of the experiment, they did not know which side had been treated. After another period of four months, during which time no petrolatum had been applied, the previously treated regions were still identical in appearance with the corresponding regions on the left side. This experience indicates that the regular and prolonged use of petrolatum does not cause the short downy hairs to become either longer or coarser, and that it does not stimulate growth of the eyebrows.

EFFECT OF SUNBURN

In many cases, what seems to be an excess amount of hair on the arms is attributed to the effect of sunburn. One frequently sees men who have calvities to a greater or less degree going bareheaded in the summer, with the hope that the effect of the sun will start a new growth of hair. With this in mind, it seemed worth while to compare hairs which were on an exposed region before and after the summer season.

The forearm was the area most convenient for the purpose. Twelve women between the ages of 18 and 25 were available as subjects for this experiment. In the spring, during the first part of May, and just before it was warm enough to go outside with the arms uncovered, samples of hair were taken in the manner previously described. An area on the back and more exposed portion of the right forearm half

way between the elbow and wrist was chosen to supply the samples. At the end of five months, the time each subject had spent in a warm climate with the forearms exposed, similar samples were taken from the corresponding area on the left arm. All the samples were then examined, first in their normal state and then after mounting on slides in balsam, and no differences either in length, diameter or pigmentation were apparent.

A somewhat similar test was afforded by three women who spent a great part of the summer in bathing. In all three, there was a very marked contrast in color between the tanned lower half of the thigh which had not been protected by the bathing suit and the upper portion which had. The lower part had been sunburned repeatedly, with resultant deepened pigmentation of the skin, while the upper part was not affected. The difference in the color of the skin was the only apparent difference, however, and the longer or more numerous hairs which one might have expected to find on the sunburned area were not there.

In another case at the beginning of the summer both arms were shaved and then during the following months one was protected by a sleeve while the other was exposed. After three months, the hair on the exposed arm was very definitely longer than on the other arm, but after another three months no difference in the hairy covering could be detected. This seems to indicate that certain stimuli, such as actinic rays, may accelerate hair development during its growing period, perhaps causing it to reach its final length at an earlier date, but that they have no effect whatever on the ultimate amount of hair produced.

EFFECT OF SHAVING

Shaving, perhaps more than any other treatment, is believed to result in marked increase of hair growth particularly in reference to thickness or stiffness. Until definite information was at hand, it did not seem desirable to ask any of the subjects to shave the face. Other regions including some on which the hair growth in the two sexes is very different were used, with the assumption that results from the face would in all probability be of a similar nature.

Three women shaved the right leg from the knee to the ankle twice a week for eight months. After four months more, which is ample time for hairs ranging from 15 to 25 mm. in length to grow out, no difference between the right leg and the left one, which had not been shaved, could be detected, with the exception that some of the shaved hairs still had blunt ends.

An area which perhaps might be expected to respond to shaving as readily as any is the hypogastric region. Hair of this region might be considered in the nature of a secondary sexual characteristic, for in

women it is of the fine, downy type, while in men it is usually well developed and similar to the pubic hair. Three women and one man shaved this area twice a week for eight months, and after allowing sufficient time for the hair to regenerate, there was in the case of the women no similarity to pubic hair and in the case of both sexes no change from the type of hair which preceded the experiment. One man and one woman shaved an area on the breast surfounding the areola and also the center of the chest, but after regeneration no change in the hair growth could be detected.

Several hairs on the leg of one of the subjects were marked by injecting gentian violet and then shaved under various conditions. Those which were growing at the average rate were shaved close to the skin, with the result that they continued to grow at the same rate. Others which had stopped growing were shaved, and in no case did regeneration begin again. In one instance, twelve weeks after the hair had been shaved off, a hair appeared, growing at the average rate, but on examination it was found to have a pointed end and consequently to be a new hair taking the place of the other one whose root must have fallen out. A few tests made by cutting hairs on the ear also indicate that, with them, too, regeneration of the individual shaft occurs, if at all, only when it is cut during the growth period.

COMMENT

It is not unusual to find women with hypertrichosis who believe that it is the result of shaving or that the degree has been increased by shaving. The fact remains that in all such cases it was the presence of the excess hair which caused its removal in the first place. One might justifiably assume that if shaving increases the size or amount of hair on a woman's face it would have the same effect in men, but there seems to be no evidence that such is the case. On that part of a man's face which is shaved, hairs of the downy type as small as those on a normal woman's face are present, and in the rare instances of men who never have shaved, the hairs of the beard may be as coarse as those in men who have shaved for many years.

Likewise, the assumption that sunburn has at best any more than a very transient effect on hair growth fails to receive any support from these observations.

In the case of petrolatum, the evidence seems clear that by itself it is incapable of affecting the growth of normal hair. Whether or not it may have any value clinically is not within the scope of this paper.

It should be borne in mind that the observations reported here are not very extensive and that they are based entirely on presumably normal persons. It is believed, however, that they do indicate that

certain widespread ideas as to hair growth do not rest on a firm basis, and that there is need for more careful work before we can know what are the real factors regulating the growth of hair.

SUMMARY

Observations on the rate of growth of hair in normal individuals are recorded.

The rate of growth of hair is different in different regions and shows a positive correlation with the cross section area.

No effect on the growth of hair from application of petrolatum, from exposure to sunburn or from shaving could be found.

REPORT OF THE COMMITTEE ON STATISTICS OF THE AMERICAN DERMATOLOGICAL ASSOCIATION FOR THE YEAR 1921

SIGMUND POLLITZER, M.D.

NEW YORK

In lieu of the customary quinquennial report covering the entire range of dermatoses, your committee, with the consent of the council, limited its inquiry this year to a few diseases whose incidence seemed of special interest. It was recognized that for most dermatoses the ratios of their occurrence have been fairly well established by the thirty-five annual reports already made. In addition to the few diseases whose incidence was recorded, an attempt was made to gather statistics on the occurrence of occupational diseases—a classification heretofore not made

CASES REPORTED FOR THE YEAR 1921

	No. of Cases	Cases Per Thousand		
		1921	1916	1898-1911
Blastomycosis	21	0.4	0.44	0.4
Epidermophytoses and trichophytoses	2,875	57.5	28.8	31.4
Epithelioma	905	18.5	21.8	13.9
Lepra	33	0.6	0.2	0.35
Lichen planus	329	6.8	6.9	4.8
Pemphigus	49	1.0	0.5	0.7
Pityriasis rosea	488	10.3	8.2	4.8
Psoriasis	1,187	22.8	36.7	26.5
Scabies	3,231	65.8	32.1	59.4
Sporotrichosis	6	0.1	0.1	....
Syphilis	8,512	172.9	131.7	94.4
Total	48,611			

in our reports—and to collect some special data on syphilis: the frequency of cerebrospinal and cardiac affections, the number of arsphenamin injections administered and the "reactions" following this treatment.

Twenty-three reports, representing the work of twenty-eight of our members, were received. The total number of cases reported for the year was 48,611. This number is smaller by 17 per cent. than the number reported in the last quinquennial report, in spite of the fact that our membership and the population of the country has increased. Table 1 shows the number of cases of the various diseases reported for the year, their ratio and a comparison with the ratios in the last report and in the combined reports for the 1898-1911 period.

A few words of comment on these figures may be permitted. The ratios of blastomycosis and sporotrichosis are almost identical with those in the 1916 report. The Middle West continues to supply our

cases of these diseases; the twenty-one cases of blastomycosis and six cases of sporotrichosis are reported from Chicago, St. Louis, Ann Arbor and Cleveland, with a few from New York. Epithelioma is represented by 905 cases, constituting 18.5 per thousand, as compared with 21.8 in 1916, and an average of 13.9 for the 1898-1911 period. This ratio, while not up to that of 1916, is still higher than the earlier average, in line with the increased incidence of cancerous diseases in general.

The epidermophytoses and trichophytoses show a large increase, 2,875 being reported, 57.5 per thousand, as against half that number in 1916 (28.8), and an average of 31.9 for the earlier period. The conclusion might be drawn that this group of diseases is on the increase; but it must be borne in mind that recent additions to our knowledge have wrought a change in our recognition of these infections, many forms of which were classified formerly as dyshidrosis or eczemas of various kinds. The apparent increase in the number of cases of leprosy is due to the inclusion in our report of the cases seen by one of our new members, resident in Cuba. The ratio of lichen planus (6.8 per thousand) shows a striking coincidence with that reported in 1916 (6.9), and this figure, roughly, about one case in 200, may be definitely accepted as representing the incidence of this disease in dermatologic practice in America.

Pemphigus, all forms, shows an increase over the previous reports; but the number of cases (forty-nine) is too small to justify any conclusions. Pityriasis rosea also shows a marked increase; 488 cases were reported, 10.3 per thousand, as against 8.2 in 1916 and 4.8 for the 1898-1911 period. This dermatosis has come to be generally recognized by dermatologists only within the last twenty years, and the conclusion that the disease is on the increase is probably not warranted. Psoriasis shows a slightly smaller ratio than our previous averages, but the difference is not significant. It may be accepted that psoriasis occurs in dermatologic practice in this country in the ratio of five or six cases in 200, a figure considerably smaller than that shown in various European statistics.

Scabies, with 65.8 cases per thousand, shows an incidence somewhat above the average for this disease, but considerably below the peak of ninety-seven per thousand in 1903. From the high point of that year the scabies curve dropped uniformly to its mean of about fifty per thousand in 1911 (annual reports ceased with that year), and in the first quinquennial report (1916) had fallen still farther, to the low figure of thirty-two per thousand. It seems to be a general impression that the number of scabies cases was greater in 1920 than the number included in the present report. If this is true, it seems probable that

a high point of possibly sixty or seventy per thousand was attained in 1920, and that the incidence of this disease is at present again declining.[1]

With regard to occupational dermatoses, concerning which it was hoped that some important data might be submitted, your committee regrets that no summary of any value is possible. Several members reported no cases at all; one member wrote that he did not make that diagnosis. One large clinic in New York reported 424 cases out of a total of about 8,000 cases (fifty-three per thousand). Another clinic in the same city reported eighteen cases out of about 5,000 (less than four per thousand). It is obvious that no adequate records were made of these cases in the majority in incidences. The matter is of importance, however, in relation to the subject of industrial hygiene and may be worth more attention than most of our clinics have given it.

Except for the total number of cases and the number of arsphenamin injections, the syphilis reports have proved rather disappointing. Some of the members did not realize that the groups, early and late cases, obviously included all cases of syphilis, but, after recording these totals, reported their number of asymptomatic, cardiac, cerebrospinal and congenital syphilis, and added these numbers to the figures for early and late cases, giving a syphilis total that left the committee somewhat confused as to their meaning.

Correcting these errors as far as possible, we have a grand total of 9,408 cases of syphilis, a proportion of 173 per thousand, as compared with 132 in 1916, and ninety-four for the fourteen-year period, 1898-1911. The conclusion from the larger proportion of syphilitic patients during the last year that there has been an increase of from 30 to 90 per cent. in the incidence of syphilis throughout the country, is, in the committee's opinion, wholly unwarranted. The general impression, indeed, seems to be that the number of fresh infections has been declining for several years. Our increased proportion of cases of syphilis may be more justly ascribed to the circumstance that patients having asymptomatic cases that were neglected in former years are today the subjects of treatment, and that the necessity for continued treatment in the absence of obvious symptoms has been impressed on the patient by the physician and the social service agencies nowadays employed by most clinics. This result of modern teaching is distinctly a subject for congratulation.

Very few of the members made any report on the reactions following injections of the arsenicals, and these few are scarcely worth compiling. It may be noted, however, that there were six cases of exfoliative dermatitis out of 2,744 syphilitic patients reported by six

1. Compare Statistical Report for 1911, J. Cutan. Dis. **32**:314, 1914.

members, a ratio of a little more than two cases per thousand. These totals are too small to justify any conclusion. One death after arsphenamin (exfoliative dermatitis) was reported. Most of the members reporting give the number of arsphenamin injections: 9,408 syphilitic patients received 58,117 injections of arsphenamin during the year, a ratio of 6.2 injections per case. The practice in different clinics varies considerably. The highest number of injections reported was twelve per case a year; the smallest number two per case a year. In the larger clinics, the number of injections were fairly uniform, averaging from six to eight per case a year.

The committee is convinced that the inadequacy of the reports received is largely due to the circumstance that the members were not notified early enough as to the nature of the information sought. The subject is of great importance, however, and a report covering the large totals that might be obtained if all our members were sufficiently interested to make careful records and reports, could well yield results of great value. The committee asks authority to renew its inquiry next year and to this end to submit a circular stating explicitly the kind of information sought in regard to syphilis and the occupational dermatoses, at the end of the current year, limiting the inquiry to these two subjects, so that the members will be prepared to gather statistics during the coming calendar year, to be submitted early in the year 1924.

Abstracts from Current Literature

REPORT OF A CASE OF DISSEMINATED GUMMATOUS SPOROTRICHOSIS, WITH LUNG METASTASIS. L. M. WARFIELD, Am. J. M. Sc. **164**:72 (July) 1922.

In this case, there were the usual ulceration and gummatous formations on the feet, legs, arms and face, the lesions yielding a sporothrix culture. Roentgen ray revealed involvement of the right lung; and attention is called to the possibility of generalization of sporotrichosis and lung involvement.

SYPHILITIC BACKACHE. W. THOMPSON, Am. J. M. Sc. **164**:109 (July) 1922.

Two cases are reported in which the only complaint was pain in the back. In one case, a roentgenogram revealed a thickening of the periosteum and bony deposits at the tenth, eleventh and twelfth dorsal vertebrae. The other case was negative. Both patients had a negative history but a strongly positive Wassermann reaction, and in both the backache was cured by antisyphilitic treatment. Syphilitic spondylitis should always be considered a possibility in all indefinite cases of backache.

QUANTITATIVE STUDIES IN SYPHILIS FROM A CLINICAL AND BIOLOGIC POINT OF VIEW. J. A. FORDYCE, ISADORE ROSEN and C. N. MYERS, Am. J. M. Sc. **164**:492 (Oct.) 1922.

This is the first of a series of articles dealing with a number of questions relating to the amount of arsenic in the blood after intravenous injection; the amount in the urine; variation in the amount; the difference after using the various preparations intramuscularly; length of time arsenic is demonstrable, and similar questions regarding arsenic and the cerebrospinal fluid. It deals with the apparatus used, reagents and tests for arsenic. Later articles will give the relation between clinical and analytic data.

THE WASSERMANN REACTION IN NONLUETIC CASES. T. MCKEAN DOWNS, Am. J. M. Sc. **164**:514 (Oct.) 1922.

The Wassermann reaction, it is stated, is always positive at some stage of syphilis but rarely positive in syphilis-free cases. Other diseases, such as malaria and tuberculosis give only weakly positive reactions when positive at all, and uncomplicated hyperthyroidism gives no positives. The author believes the cholesterinized antigen invaluable in following cases in which patients are under treatment, but which are too sensitive for diagnosis without a definite history or symptoms.

STUDIES OF CEREBROSPINAL FLUID AND BLOOD OF SYPHILITIC AND NORMAL PERSONS, WITH SPECIAL REFERENCE TO THE IMMUNITY REACTIONS AND THE COLLOIDAL GOLD TEST ON THE ORIGINAL AND UNFILTERED FLUIDS AND SERUMS. C. E. NIXON and K. NAITO, Arch. Int. Med. **30**:182 (Aug.) 1922.

From these studies, the authors conclude that positive colloidal gold reactions are due to the presence of precipitating substances which, with protecting

substances, are present in pathologic spinal fluid. Albumin and globulin can be both precipitating and protective, but, when syphilitic and normal serums are ultrafiltered, their curves are more or less similar, the difference being more marked with the syphilitic than with the unfiltered serum. The protective action is partially neutralized by salt solution and by ultrafiltration, while both precipitating and protecting powers are modified by the state of the protein.

JAMIESON, Detroit.

OBSERVATIONS ON TRICHOMYCOSIS AXILLARIS FLAVA, RUBRA AND NIGRA. ALDO CASTELLANI and A. GEDEN WILKINSON, Brit. J. Dermat. & Syph. **34**:225 (Aug.-Sept.) 1922.

During investigations on the frequency of trichomycosis axillaris in patients admitted to the tropical section of the Orpington Hospital, the authors found that more than 80 per cent. admitted during the summer were affected with this disorder. In the hospital cases, only the yellow variety was found; while, among private patients, in addition to the yellow variety, two cases of the red and one of the black variety were seen. Most of the patients seemed to have contracted the affection in tropical or subtropical countries, but it was found also in individuals who had never been out of England or France.

Castellani has described three types of trichomycosis—the yellow variety, due to a fungus which he called *Nocardia tenuis;* the black variety, due to the same fungus plus a black pigment producing coccus which he called *Micrococcus nigrescens;* and the red variety, due to the same fungus plus a red pigment producing coccus, *Micrococcus castellanii.* The microscopic and cultural characteristics of these various organisms are then given in detail.

It appears that, when the nocardial fungus first attacks the hair, it grows and pushes its way under a cuticular scale. It then works its way into the cortex, in so doing, raising its superficial fibers, which, together with the cuticular scale, form a covering or protection for the fungus, which probably finds its nutriment in the cortex. The fungus does not penetrate very deep into the cortex, but grows outward, forming the characteristic nodules. This method of growth explains why the hair is affected so little, though at times it loses its luster.

Clinically, the affected hairs of the axilla and pubes present nodular formations, yellow, black or red, depending on the type of infection. In the tropics, the nodules are of a rather soft consistency and are easily removed; while, in temperate zones, the nodules are such smaller, and difficult to remove.

The infection generally appears to be from man to man. In acute cases, the skin of the axillae may be erythematous, and hyperhidrosis is a common complication. As long as the patient resides in a tropical country, there is no tendency to spontaneous cure; but the condition may subside or disappear completely if he goes to a cold climate. An efficacious method of treatment consists of dabbing the axillae twice daily with 1 dram (3.7 c.c.) of liquor formaldehydi to 6 ounces (178 c.c.) of alcohol, while at night a 2 to 5 per cent. sulphur ointment is rubbed in. Tincture of iodin is useful in obstinate cases, after a few days of the foregoing treatment.

A SPECIALIZED FAVOID SCALP CONDITION PECULIAR TO THE SYPHILITIC NATIVE OF SOUTH AFRICA. A. REITH FRASER, Brit. J. Dermat. & Syph. **34**:267 (Aug.-Sept.) 1922.

Fraser describes a condition seen only in the scalps of syphilitic South African natives, by whom it is called wit kop, dikwakwadi or white head. It

appears to be most prevalent in British Bechuanaland, where the native population is extensively syphilized, although the great bulk of the syphilis is of the hereditary type. Among these people, "wit kop" is so frequent and consistent that it has come to be considered a specific manifestation of heredosyphilis in the degenerate Bechuana.

The condition begins with the appearance of a number of isolated lesions on an apparently healthy scalp. These macules have the usual characteristics of syphilitic macules, and are slightly raised and almost colorless. They appear irregularly, and have no relation to hair follicles. They develop into papular types, notable because of their noninflammatory character. Coalescence begins in the papular stage, and is well advanced with the pustular stage. The pustule soon shows a marked tendency to crust formation, the crust being dry and friable, and made up of layers. By coalescence of these dead white to yellowish white crusts, the scalp becomes covered with a thick dry dirty white crust, and is totally devoid of hair except around the nape of the neck and in front of the ears.

The condition resembles favus, but, according to the author, is readily differentiated. Although a fungus has been described as being found in a few cases, the author is convinced that it cannot be regarded as the etiologic factor, while its direct connection or association with spirochetal affection cannot be disregarded.

In untreated patients, there is a slow chronic unresolving course, with a marked tendency to relapse; but consistent combined antisyphilitic treatment causes a rapid disappearance of "wit kop."

THE ASSOCIATION OF EYE LESIONS WITH ROSACEA. R. Cranston Low, Brit. J. Dermat. & Syph. **34**:275 (Aug.-Sept.) 1922.

Struck by the frequent association of rosacea with keratoconjunctivitis, which, he states, is a condition well known to the ophthalmologist, but apparently not so familiar to the dermatologist, Low discusses the eye changes present in these cases. Blepharitis, conjunctivitis and keratitis, separately or combined, are seen. The blepharitis manifests itself as a slight scaling, which Low believes is due to seborrhea.

The conjunctivitis may be of two types, the first a noncharacteristic form, with slight redness of the mucous membrane. The palperal conjunctivae are chiefly affected here, and the picture is due to the presence of numerous dilated capillaries. The second type is less common but more severe, appearing as a number of small raised papular lesions, pin-head sized, greyish, and surrounded by a ring of minute dilated capillaries. The lesions usually occur on the bulbar conjunctivae. The lesions resemble closely those of phlyctenular conjunctivitis. These two types of conjunctival lesions usually occur together, and in most cases a scaly blepharitis is also present. The keratitis occurs in rosacea in three forms; a mild form, with ulceration of the cornea with surrounding infiltration; a severe form, with ulceration and subepithelial infiltration, and the severest form of all, with a progressive inflammation of the cornea resembling rodent ulcer. Low thinks that the skin and eye lesions are etiologically identical. The incidence of eye lesions does not depend on the severity of the rosacea, as most cases with eye lesions seem to show the milder type of rosacea. A 1 per cent. ichthyol-zinc ointment or a

1 per cent. sulphur-salicylic acid ointment gives the best results in the treatment of the lid lesions; while the treatment of the rosacea is also said to have a beneficial effect on the lesions.

SENEAR, Chicago.

THE CAPILLARIES OF THE EXTREMITIES IN ACROCYANOSIS: BLOOD PRESSURE AND MORPHOLOGY. E. P. BOAS, J. A. M. A. **79**: 1404 (Oct. 21) 1922.

In patients with vasomotor disturbances of the extremities, the capillary blood pressure in the fingers is low and the capillary flow is retarded during the period of ischemia or cyanosis. With the return of a normal color to the hands, the capillary pressure, as well as the flow, rises and approaches the normal. In most of these patients, the capillaries of the fingers are longer and wider than in healthy persons, and often exhibit many convolutions and a bizarre architecture.

NEUROPATHIC ARTHROPATHIES—CHARCOT'S SPINE. JOHN RIDLON and E. J. BERKHEISER, J. A. M. A. **79**:1467 (Oct. 28) 1922.

The authors report twelve cases of this apparently rare affection. The lesion in all their cases was in the lumbar spine. As a rule, the condition comes on quickly and without pain. The differential diagnosis is discussed at some length. A corrective jacket, in addition to specific treatment, is advised.

LEUOPLAKIA BUCCALIS. H. H. HAZEN and E. J. EICHENLAUB, J. A. M. A. **79**:1487 (Oct. 28) 1922.

As a result of their own experience and that recorded in the literature, the authors conclude that rough teeth, by causing mechanical irritation, inaugurate the vast majority of cases, syphilis and tobacco being accidental rather than causative factors. They advocate the actual cautery as the best therapeutic measure.

PENILE CHANCRE WITH RINGWORM: REPORT OF CASE. E. J. EICHENLAUB, J. A. M. A. **79**:1518 (Oct. 28) 1922.

The patient had an indurated scaly lesion of the penis, in which fungi were demonstrated. A dark-field examination was negative. Later, secondary syphilitic manifestations appeared. Eichenlaub believes the ringworm fungus was a secondary invader.

MICHAEL, Houston, Texas.

A REPORT FOLLOWING THE USE OF MERCUROSAL IN THE TREATMENT OF ONE HUNDRED AND FIFTY CASES OF SYPHILIS. W. E. KEANE and J. G. SLAUGENHAUPT, J. Urol. **8**:197 (Sept.) 1922.

The advantage of larger doses, absence of local reactions and increased frequency of administration are claimed for this preparation in comparison with other mercurials. Experimental work demonstrated that only a small portion of the mercury administered passed through the kidneys and necropsy revealed that no damage had been done to the kidneys or to any other organs by the mercurosal.

Contact with alcohol, ether and heat does not increase the toxicity of the preparation.

JAMIESON, Detroit.

THE PRESENT STATUS OF RADIUM THERAPY. E. S. LAIN, South. M. J. **15**:495 (June) 1922.

The author testifies to the value of radium in the diseases in which it is indicated by common consent. He believes that radium will eventually become the treatment of choice in cancer of the lips and mouth.

MICHAEL, Houston, Texas.

THE FIRST CONGRESS OF FRENCH SPEAKING DERMATOLOGISTS AND SYPHILOLOGISTS. Presse méd. **30**:559 (July 1) 1922.

The Epidermomycoses. Presented by Petges of Bordeaux.

Intertrigoid Epidermomycosis: Besides the streptococcic intertrigo of Sabouraud, there are some intertrigos of mycotic origin, first observed in the inguinal folds and described by Whitfield, in 1908. We owe the discovery of *Epidermophyton* (1910) in these lesions to Sabouraud. Clinically, one cannot clearly differentiate true intertrigo, streptococcic intertrigo and mycotic intertrigo.

The intertrigo due to the yeasts resembles closely *Epidermophyton intertrigo*. The yeasts found are *Saccharomyces, Endomycosis albicans* and the cryptococcus.

The intertrigo due to *Epidermophyton inguinale* is poorly outlined; it has numerous satellite lesions beyond the periphery; it is humid and glistening, more or less infiltrated, with sometimes a white creamy surface, indicating a certain degree of maceration. It frequently has minute vesicles on the borders or arranged in groups. The *Epidermophyton* type is midway in appearance between the dry streptococcic type of Sabouraud and the impetiginous or purulent stage.

Diabetics: Those suffering from diabetes are prone to develop *Epidermophyton* intertrigo, owing to the dampness and heat in the affected regions, which are impregnated with sugar.

Eczematoid Epidermomycosis: At times the *Epidermophyton* eruption may be recognized clinically, but there are numerous cases of true eczema that cannot be differentiated from *Epidermophyton* intertrigo without the aid of the laboratory. The intertrigo due to yeast must also be ruled out, but only by the laboratory.

Sporotrichum perhaps plays a rôle. Dubreuilh and Petges reported a case of mycotic eczema extending from the neck to the feet; it resembled true eczema so much that its etiology was obscure for several months. It was finally discovered to be due to *Sporotrichum beuermanni*. There was nothing suggestive of deep sporotricosis.

Dr. Petges has noted several cases which strongly resembled seborrheic eczema. The eyebrows, forehead and lids were involved, and on culture a *"Trichophyton gypseum-asteaoides"* was found.

Dyshidrosiform epidermomycosis: Recent work by many investigators has proved conclusively that the malady of T. Fox and Hutchinson may frequently be mycotic or due to yeasts. However, there is undoubtedly a true dyshidrosis, due, perhaps, to some artificial cause. The parasite of the mycotic dyshidrosis is found on the top of the vesicle and not in the fluid.

Various Types of Epidermomycosis: Du Bois believes certain related types of pityriasis rosea are due to a parasite. This recalls Hebra and Vidal's theory and work. They thought that it was due to *Microsporon roseum*, and that it was infectious.

Keratotic Types: The old hyperkeratotic eczema of Dubreuilh is now believed to be caused by a cryptococcus (*Cryptococcus mymecial*). There are

also some epidermomycoses of psoriasiform, parakeratotic and syphiloid types. The author observed a child covered with psoriasiform parakeratotic plaques due to *Achorion schönleinii.*

Erythematous and Infantile Dermatitis Types of Epidermomycosis: Some cases of erythematous, erythematosquamous and infantile dermatitis are of mycotic origin. Yeasts are also believed to be responsible for a number of cases of the foregoing types. Dr. Petges classified the parasites and yeasts most commonly found.

The therapy of epidermomycosis is important. Iodin, chrysarobin and Whitfield's ointment may cure it, but if *Epidermophyton* is planted on a true eczema, the condition may become worse. One must also remember that some of these cases are due to the staphylococcus, streptococcus or mixed organisms, and here a real question of therapy enters.

Discussion.—A Vesicopustular Form of Mycotic Intertrigo of Dubreuilh: Favre (of Lyon) described an epidermophyton intertrigo of the folds which was vesicobullous in character. It was quite pruritic, and its location made one think of dermatitis herpetiformis. On examination of the scales and cultures, the parasite was found to resemble yeast. The condition was cured quickly by iodin.

Epidermomycosis Due to "Trichophyton Rubrum": Montlaur and Dumet reported a case of circinate, polycyclic inguino-crural lesions with a series of concentric circles. The parasite was *Trichophyton rubrum* or *purpurum* of Castellani-Bang (1910).

Lesions of the Glabrous Skin Produced by Microsporon Audouini: Pautrier and Reitmann (of Strasbourg) have observed in schoolchildren, 160 cases of disease of the scalp and thirteen cases of disease of the body caused by microsporon; the plaques were single and multiple. Cases of this kind are rare, because it is well known that tinea capitis is commonly due to *Trichophyton* and occasionally to some *Miscrosporon* of animal origin, such as *Microsporon lanosum.*

A Case of Epidermomycosis Due to "Mucor Ramosus": Spillman and Lasseur (of Nancy) report an observation on a patient presenting some erythematosquamous lesions on the neck and forearms, arranged in placards, recalling herpes circinatus. The lesions soon lost their superficial characteristics; the epidermis became thickened and covered with pustules, soon followed by deep ulcerations, covered with yellowish pus, resembling dermatitis vegetans. Cultures were taken from the pus. They contained *Mucor ramosus,* closely akin to *Mucor corymbifer.*

A Dyshidrosiform Epidermomycosis Due to a "Cryptococcus": Burnier and Langeron had observed in a woman of 70 years a squamous lesion between the toes and on the plantar surface of right foot, which had been present for six months. Examination of the scales revealed spores, and a pure culture contained yeast forms. They called the parasite *Cryptococcus jeanselmei.*

Researches on the Mycotic Origin of True Dyshidrosis and Some Dyshidrosiform Eruptions: Legrain pointed out that according to some works of Darier and Mlle. Iliascheff the origin of dyshidrosis is either mycotic or artificial. They examined thirty-two cases of lesions on the hands and feet characterized by dyshidrotic vesicles. These types of dyshidrosis were found: (1) True, typical dyshidrosis or the malady of T. Fox was most frequent (eighteen cases out of thirty-two). Research and culture for parasites were always negative. (2) Dyshidrosiform eruption from various causes: some had an internal cause—visceral lesions or intoxication (seven cases); the others an

external cause—artificial (two cases) or mycotic (five cases). Epidermomycoses resembling dyshidrosis, especially frequent on the feet, but which may exist on the hands. In these cases it is necessary to find the parasite.

Etiology of Dyshidrosis: Milian is of the opinion that dyshidrosis is a syndrome of syphilis. It responds readily to antisyphilitic treatment.

Renault cannot admit the syphilitic etiology of dyshidrosis because the vesicular syphilid is a rare condition. When it occurs in a syphilitic person, it is a coincidence.

Brocq considers dyshidrosis a well-defined morbid entity which usually appears in springtime. He does not consider true dyshidrosis of mycotic origin, and believes that it should be differentiated from the dyshidrosiform dermatosis, which can be proved to be due to external pathogenic agents. Thibierge supports Brocq's opinion.

Darier and Mlle. Iliascheff found mycelial parasites in 80 per cent. of the cases in which the clinical aspect was that of dyshidrosis.

Gougerot has observed ninety-seven cases of dyshidrosiform epidermomycoses in eight years; twelve times, he found yeasts in the lesions; twenty-seven times, some fungi other than yeasts; in the other cases, he was unable to find anything.

Ravogli (of Cincinnati) believes that true dyshidrosis has nothing to do with mycotic conditions; he considers it of angioneurotic origin.

Bloch (of Zurich) believes that one should differentiate between dyshidrosis of the hands and feet; the hands rarely show fungi, while the feet frequently do. With cultures of fungi, the author has been able to reproduce some elementary lesions of dyshidrosis on himself.

Peyri (of Barcelona) considers dyshidrosis as an individual cutaneous reaction. In some patients, any general cause may produce the dyshidrosis as an individual cutaneous reaction. It is thus that he has observed this affection after the administration of arsphenamin. Occasionally fungi are present, which the author considers only as an accessory element, because he has never been able to reproduce the lesions experimentally.

Horta (of Rio de Janeiro) points out that in Brazil one frequently finds, side by side, true dyshidrosis, dyshidrotic dermatosis or dermatoses caused by some yeast or trichophyton, especially by *Trichophyton rubrum* or *purpurum* of Castellani; in other cases, one finds nothing.

Sabouraud says that he is certain that some conditions called dyshidrosis are mycotic, and vice versa. The mycotic lesions of the fingers present one fourth to one half a circle, sufficiently recognizable to distinguish true dyshidrosis

True Intertrigo: Dubreuilh (of Bordeaux) believes that true intertrigo is due to friction; he has observed it appear on the internal thighs after a day of marching and disappear after a night's rest. It was hot, red, swollen and painful.

Queyrat does not admit that intertrigo is a dermatologic entity; he considers the characteristics of an intertriginous lesion as one situated between two surfaces which rub against each other; he prefers to differentiate between an intertriginous erythema, an eczema and an erythematous psoriasis.

Ravogli says that it is difficult to differentiate a simple intertrigo due to friction from one due to the epidermophyton.

Mycotic Etiology of Pityriasis Rosea: Du Bois (of Geneva) has encountered in some erythematous dermatoses of the type of pityriasis rosea of Gibert,

a fungus, *Microsporon dispari;* but the clinical diagnosis is difficult to establish between the different forms of generalized pityriasis. It is difficult to find the parasite, and the culture cannot be made from it.

Sabouraud thinks that the spores found by Du Bois were not those of true pityriasis rosea but of some eruption simulating it.

Hyperkeratotic Forms of Epidermophytosis: W. Dubreuilh draws attention to the trichophytosis on the palm of the hands which makes the palms a little dry and wrinkled. The lesions are unilateral or bilateral and bear no relation to the profession of the patient.

Epidemics of Epidermophytosis: Halle has observed an epidemic of marginal eczema of Hebra in the sanatorium for tuberculosis of Bligny. The epidemic lasted a year. One is unable to combat it; it ends by extinction; the mode of contact remains obscure.

Sabouraud has reported some endemo-epidemics of epidermophytosis in young children of the upper classes. Seventy-five cases were noted in two years. Efforts to control these epidemics in young children were made for three years before the condition could be stopped.

Du Bois points out that pityriasis versicolor is frequent in pregnant women but disappears spontaneously with the end of pregnancy.

Br. Bloch notes the frequency of oidiomycoses in the diabetic. He proves this point experimentally in the dog.

Flandin calls attention to the rôle of sensibilization. Dyshidrosis attacks certain subjects and appears in them periodically. The lesions may survive after the disappearance of the parasite. For desensibilization, sodium hyposulphite, autoserotherapy, etc., are indicated and give good results.

DIVERSE COMMUNICATIONS

Statistics of Contagious Syphilis Observed in Parisian Prostitutes from 1910 to 1921.—Bizard and Bralez have noted that the percentage of women with contagious syphilis has a tendency to increase rather than diminish. This is not due to laxity on the part of the antivenereal clinics; he suggests, however, that a closer surveillance of the prostitute should be observed.

Carle (of Lyon) believes the number of prostitutes having contagious lesions is diminishing, as shown by his statistics.

Preventive Treatment of Syphilis During the Incubation of the Chancre.—E. Bodin (of Rennes) has treated five healthy women who have been exposed to infection either from a chancre or secondary genital lesions. These women received a single series of from four to six intravenous injections of neoarsphenamin. None of the five was infected, as shown clinically and serologically. Many others have reported similar results, and it has proved of assistance to those exposed.

Carle (of Lyon) says that he knows of eight of eleven patients who were exposed by syphilitic women, and who never contracted syphilis. They used no prophylactic measures. Carle warns against these premature reports filtering through into the daily press.

Pigmentations, Depigmentations and Cutaneous Atrophies Among Syphilitic Patients.—Payenneville (of Rouen) reports six observations: three cases of pigmentation of healthy skin in the secondary period, with the phenomena of suprarenal insufficiency; and three cases of vitiligo in two of which the lesions appeared in a syphilitic during the evolution of the eruption, and in

one of which it occurred before the secondary eruption appeared. These observations point to an involvement of the suprarenal, which coincides with Br. Bloch's theory as to the cutaneous pigment.

Intravaginal Chancre. Prolongation of Duration of Incubation Following Injection of Neo-Arsphenamin Given Thirteen Days After Suspicious Intercourse.—Paul Meynet (of Nice) reported a case of a woman who had intercourse, Feb. 6, 1922, with a subject having a suspicious lesion on the penis. On Feb. 19, 1922, tests made on the woman were negative; she received, at this time, one injection of neo-arsphenamin; on May 12, 1922, ninety-three days later, she returned with an ulceration on the left vaginal wall in which spirochetes were found; the Wassermann test was negative. The man was examined and found to have had chancre on the right side of the penis. It is interesting to note the location of the chancre and the long period of time before development. Had more neo-arsphenamin been given, the condition would have probably been aborted.

The Leper and Mode of Transmission.—J. Peyri (of Barcelona) lays much stress on the mode of transmission in lepers at the leper houses. The author has placed some fragments of leproma on inanimate objects and established the existence of Hansen's bacilli some time later. The author believes that there exists in all cases a cutaneous or mucous condition which opens the channel for contagion, even in the nervous form.

He gives the name "leprous chancre" to all localized leprous lesions of long duration; when one notes a generalized eruption it is usually hereditary in origin, or there is an intestinal chancre.

Partial Scleroderma Treated Successfully by Associated Opotherapy.—Hugel (of Strasbourg) presented a case of scleroderma of the foot and calf of the leg which disappeared entirely under the administration of thyroid, ovarian, hypophysial and suprarenal preparations. He noted scleroderma with the same frequency as goiter in Alsace.

Autohemotherapy in Dermatology.—Nicolas and Gaté (of Lyon) have had remarkable success with thermotherapy in cases of prurigo, papulovesicular eczema, Duhring's disease and especially furunculosis; on the other hand, in lichen and ordinary eczema Spillmann (of Nancy) and Laureut (of Saint-Etienne) have had the same success with this method in pruritis and prurigo.

McCafferty, New York.

THE ETIOLOGY OF HERPES SIMPLEX. A. Fontana, Gior. ital. d. mal. ven. **63**:96 (May) 1922.

From his experimental work, the author concludes that it is possible to inoculate the virus of herpes on the skin of another person; that it is possible to autoinoculate the virus of herpes on the arm of the patient himself, and that the virus of keratitis herpetica of the rabbit, when inoculated in the human skin, reproduces typical lesions of herpes.

EPIDEMIC PEMPHIGUS. M. Trosarello, Gior. ital. d. mal. ven. **63**:98 (May) 1922.

The author reports thirty cases of a bullous dermatitis, twenty-six of them occurring in children under 13 years of age, living in one community. He reports eleven other cases disseminated in the surrounding villages. The dis-

ease ran a course of from two to four weeks, new outbreaks of bullae appearing every three or four days. In children, there was pronounced general disturbance and a thermic reaction reaching 38 C. (100.4 F.). No fatalities occurred.

CHANCRE OF THE EAR. L. Morini, Gior. ital. d. mal. ven. **63**:101 (May) 1922.

The patient had a furuncle situated in the tragus. About fifty days afterward, a syphilitic chancre developed on the scar. Syphilitic chancre of the ear is rare, representing about 2 per cent. of all extragenital chancres.

CYLINDROMA OF THE SKIN. D. Majocchi, Gior. ital. d. mal. ven. **63**:122 (May) 1922.

Report is made of a case of a small tumor of one year's duration, situated on the right eyebrow of a man 38 years old. Xanthoma tuberosum was given as a probable diagnosis, on account of its yellowish color. Teratoma and fibroma were also considered. Pathologic examination proved it to be a typical cylindroma.

GRAIN-MITE DERMATITIS. D. Majocchi, Gior. ital. d. mal. ven. **63**:124 (May) 1922.

The city and district of Bologna have been infected with grain-mite, producing dermatitis, for many years. Majocchi reports about 300 cases of the condition in the year 1921. The eruption is the typical erythematopapular or papulovesicular dermatitis produced by pediculis ventricosus. Epidemics are common in jails and asylums.

CIRCUMSCRIBED ANGIO-ECTATIC ERYTHRODERMA. D. Majocchi, Gior ital. d. mal ven. **63**:134 (May) 1922.

A girl, 17 years old, presented numerous patches of erythematopapular, desquamating erythroderma. A peculiar feature was the presence of numerous dilated capillaries on the affected areas. The blood pressure was 220. Thyroid extract therapy reduced the pressure to 180, and the cutaneous condition improved at once. The condition seems to be due to an endocrinous disturbance causing increase of the blood pressure.

BOWEN'S PRECANCEROUS DERMATOSIS. L. Martinotti, Gior. ital. d. mal. ven. **63**:182 (May) 1922.

Many dermatoses present atypical epithelial changes that may be considered precancerous, and indeed many cases of epithelioma develop on old scars of lupus vulgaris, lupus erythematosus, radiodermatitis, psoriasis, varicose ulcers and syphilitic scars. The author thinks that eczema precedes the development of Paget's disease and of Bowen's precancerous dermatosis. The first case reported by Bowen, in 1919, was one of epithelioma developed from an arsenical keratosis implanted on a chronic eczema. Two cases of Bowen's disease are reported, in both of which the lesions were situated on chronic eczematous patches. The differentiation between Paget's and Bowen's conditions is fully considered.

V. Pardo-Castello, Havana.

CARBON DIOXID SNOW THERAPY. PAVEL BEUTL, Ceska Dermat. **4**:1, 1922.

Pusey's carbon dioxid snow treatment has been tried out with good results at the skin clinic in Brüun. The lesions of the face were especially benefited by this method. Freezing alone has been used in cases of simple vascular and pigmented nevi, lupus erythematous, keloids and cases of epithelioma. Several cases in which patients were treated by combined methods are reported. An extensive verrucous linear nevus was previously treated by Unna's digestive fluid to remove the horny masses; in a hemifacial cavernous hemangioma, the external maxillary artery was ligated and freezing was then combined with electrocautery; in nine cases of epithelioma, the patients were exposed to roentgen rays a day after freezing (two recurrences). In lupus vulgaris (ninety-two cases), the tubercles were at first disintegrated by means of Finsen light or by electrocautery, and then freezing was employed to bring on a more rapid resorption of newly formed pathologic tissue and a better scar. In lupus vulgaris of the face, the author favors the combination of freezing with the sodium chlorid method as used by Jadassohn.

BISMUTH—THE NEW ANTISYPHILITIC REMEDY. VICTOR SEDLAK, Ceska Dermat. **4**:10, 1922.

At the clinic in Bratislav, "Trepol," tartrobismuthate of potassium and sodium in oil suspension has been given a trial. Seventy-six patients having syphilis in various stages were treated. A course consisted of from ten to twelve intragluteal injections: first, two of 2 c.c. each, two days apart; then three 3 c.c. doses, three days apart; finally doses five or six days apart, as the infiltrate disappears more slowly. The drug seems well tolerated. Gingivitis often develops, but it was never so severe as to interrupt the course of treatment. The lesions promptly disappeared. In some cases—presenting mucous lesions and late manifestations—the healing was more rapid than ever noticed under arsphenamin or mercury. In its direct spirocheticidal effect, the bismuth is superior to mercury but inferior to arsphenamin.

A COMPLETE OBSTRUCTION OF BRONCHUS CAUSED BY A GUMMATOUS PROCESS. F. SVOBODA, Ceska Dermat. **4**:15, 1922.

Report is made of a case of a complete obstruction of the left bronchus 1 cm. below the bifurcation of the trachea. No air was entering the left lung, and the patient suffered from extreme dyspnea. He also showed an undermined ulcer with lardaceous base on the right shoulder. Administration of potassium iodid resulted in a complete cure.

SPINKA, St. Louis.

Society Transactions

PITTSBURGH DERMATOLOGICAL SOCIETY

Sept. 28, 1922

W. H. Guy, M.D., *President, in the Chair*

PEMPHIGUS. Presented by Dr. Burke.

A boy, aged 12, was first seen two weeks before, when he presented two areas of bullae, one on the anterior side of the neck and the other in the right axilla. Each area contained ten or twelve pea-sized, tense bullae containing clear serum. These areas had persisted for three years, the bullae rupturing in a day or two and new ones forming. The areas were mildly erythematous, and there was no pustular involvement and no bad odor. He would occasionally have a bulla on the body or legs, but on these locations they always healed in four or five days. The lesions healed with potassium arsenite solution (Fowler's solution) internally and Burow's solution externally. No new lesions had appeared in ten days. The urine showed a trace of sugar.

DISCUSSION

Dr. Crawford asked whether Dr. Burke considered this a chronic pemphigus of a serious type, as he felt this was a type occasionally encountered in children and was probably a toxic disturbance similar to a bullous erythema multiforme. He agreed, however, with the diagnosis.

CARCINOMA IN SYPHILITIC. Presented by Dr. Hollander.

A woman, white, widow, aged 68 years, married forty-two years, having seven miscarriages and six living children, presented lesions beginning with a pustule on the bridge of the nose fourteen years ago, which would appear and disappear. Six months later ulceration began, which was crust covered. After a course of roentgen-ray treatments the lesions disappeared. A few months later the crust formation reappeared and again responded to roentgen rays. One year later it reappeared. Of eight blood Wassermann tests, three were positive. A short course of antispecific treatment did not influence the lesion. At present the ulceration has destroyed the larger portion of the nose and is surrounded by a hard, pearly border. A brownish crust which covers the lesion separates easily, leaving a bleeding surface.

PAPULAR DISEASE OF AXILLAE AND PUBIS (Fox-Fordyce Type). Presented by Dr. Wertheimer.

A young woman, aged 20, five years ago noticed a pruritus in both axillae, followed by a papular eruption, first in the left axilla two years before, and in the right axilla one year later. One year ago, the nipples became pruritic. This condition was followed by a papular eruption. For the last six months, the pubic region had been pruritic, but free from lesions. There had been

no response to any form of treatment. Both axillae showed pinhead to large pea-sized papules (newest lesions about follicular openings and reddish) seated on a somewhat infiltrated, thickened skin. The older lesions were closely set and some coalesced forming plaquelike areas of a brownish hue. The surrounding skin showed a faint brownish yellow pigmentation. About the nipples were a few pinhead-sized excoriated papules with slightly increased pigmentation.

PEMPHIGUS CHRONICUS. Presented by DR. CRAWFORD.

A physician, aged 62, who had always enjoyed good health and who had good habits, two and one-half years ago had various sized bullae in the pharynx, the coverings of which became separated and would be coughed up and expectorated, leaving raw surfaces which at times caused a partial aphonia and dysphagia. This condition continued for more than a year with intermittent recovery and relapse. Three months after the onset of bullae in the pharynx, there occurred over the auricular helixes and later about the nasal orifices and at the angles of the mouth bullae which were at first small and tense and which rapidly developed in size from 0.5 to 1 cm. or larger, when they became flaccid and the contents seropurulent, later drying up and disappearing, leaving a flat, reddish area, which finally disappeared. Similar lesions had occurred over the back of the neck and over the dorsal surfaces of both hands, at times on the forearms and ankles, and recently over the femoral triangle of the right thigh, the latter being accompanied by a right inguinal adenitis. The lesions sprang up over night and developed into large flat bullae in a few hours, often coalescing. The patient usually noticed a local tingling just preceding their appearance. Occasionally they had developed beneath the nail. Several were hemorrhagic, the serous contents having a reddish tinge. The hands had been involved continuously for two years, pinhead sized bullae developing over the dorsa bilaterally. After reaching about 3 to 5 mm. in diameter in a short time, they subsided by first flattening and then forming a thin crust which disappeared after a few days, leaving a temporary reddish stain. There had never been any lesions on the conjunctivae or on the trunk. There was no tendency to grouping, no accompanying pigmentations, and the lesions were free from all subjective sensations. The only drugs ingested were sodium phosphate and cascara sagrada; thus the possibility of a pemphigoid drug eruption was eliminated. All physical and laboratory findings were normal.

EPIDERMOLYSIS BULLOSA. Presented by DR. WILLARD.

A girl, aged 11, had since birth developed blebs of various sizes on any part of the body exposed to heat, friction or pressure. These became hemorrhagic with severe traumatism. During cold weather the affection was almost entirely absent. A brother and sister aged 8 and 5, respectively, were similarly affected. Her mother, aged 29, was likewise affected but was becoming less susceptible. One uncle and his six children were affected. Another uncle and his nine children were not affected. Both aunts were affected, and of the ten children of one of them, nine were affected. The patient's grandfather on her mother's side was affected and of his four brothers and sisters, two were affected. The great grandmother had the first known case in this family. Descended from her were thirteen unaffected and twenty-seven affected persons.

NEUROSYPHILIS WITH AN ASSOCIATED PURPURA. Presented by Dr. Schwartz.

Mrs. G. aged 52, a large well-nourished woman, presented many symmetrical purpuric lesions on the lower extremities. These began as small petechiae and spread eccentrically, becoming as large as 3 inches in diameter. The first lesion was noted four years before, at which time she was under treatment for secondary syphilis. The original purpuric spots persisted, new ones developing gradually. Examination of the cerebrospinal fluid revealed a positive Wassermann reaction, a trace of globulin, and twenty-six small lymphocytes.

DISCUSSION

Dr. Crawford said he felt that the purpura was not dependent on the neurosyphilis, but that it was due to a food or drug toxemia, and that on account of the presence of brownish pigmentation and punctate petechiae Schamberg's disease should be considered.

Dr. Wertheimer said he believed another disease was beginning, as he noted the dilated blood vessels. He could see no relation of the purpura to the neurosyphilis.

Dr. Guy agreed with Dr. Crawford that it was an unassociated purpura.

LICHEN PLANUS SCLEROSIS ET ATROPHICUS. Presented by Dr. Schwartz.

Miss G., a robust adult woman, presented numerous atrophic lesions over the neck, chest and back. The individual lesion consisted of a small shiny whitish plaque and presented a marked increase in the normal cleavage lines of the skin. The condition was of four years' duration. It had first appeared on the neck, and gradually extended to the chest and back. The condition responded readily to the combined use of mercury and the roentgen ray.

PITTSBURGH DERMATOLOGICAL SOCIETY

Nov. 2, 1922

W. H. Guy, M.D., *President, in the Chair*

SCLERODACTYLIA. Presented by Dr. Beinhauer.

A woman, aged 34, married ten years, had had influenza in 1918, which was followed by paleness, stiffness and numbness of the left hand. Four months later she had noticed a tightness of the skin of both hands and forearms to the elbows, and she complained of rheumatoid pains. One year later she noticed brownish spots about the face and neck which were accompanied by tenseness, pallor and loss of expression. Her feet were likewise affected. During the last six weeks she had had an eczematoid eruption on both cheeks. Neurologic examination for syringomyelia and areas of anesthesia was negative. The blood pressure was: systolic, 102, diastolic, 72. The Wassermann blood test was negative. A radiogram of the chest was normal, and of the head showed a somewhat smaller than normal sella turcica.

ULCERATIVE TERTIARY SYPHILODERM. Presented by DR. GUY and DR. JACOB.

A salesman, aged 32, had had an ulcerative dermatosis involving the left side of his nose for five months. A shallow ulcer involved the junction of the mucous membrane of the nose and the skin surface of the left ala nasi. Two healed excavated scars were present on the skin surface of the side of the nose, and there was a superficial ulcer about 1 cm. long by 0.5 cm. wide just above these. A history of syphilis was denied and the Wassermann test had been negative three months previously. An irregular adenopathy was present, but other clinical signs were absent.

DISCUSSION

DR. CRAWFORD said that he regarded the condition as a tuberculosis verrucosa cutis in that there was little infiltration, the surface of the ulcerated areas was dry and granular, and the edges were irregular in outline. He felt that sporotrichosis should be considered and an attempt made to find and cultivate the fungus.

DR. GUY said that all cultures were negative, and that the condition had resisted all forms of treatment.

NOTE: A subsequent blood Wassermann test was negative, and the lesion healed under antisyphilitic treatment.

DERMOID. Presented by DR. CRAWFORD.

A man, aged 28 years, barber, presented a rounded, pea-sized, deeply situated mass on the left side of the nose about 1.5 cm. below the base. It was elevated about 5 mm. and was about 8 mm. in width. To the touch, it had a resilient hardness and was freely movable with the skin. The surface was red and traversed with dilated capillaries. The epiderm was apparently normal. Nothing could be expressed when the lesion was punctured. The patient said that the condition began three years previously as a minute "lump" which disappeared after six weeks, and that after a lapse of eight months it recurred for another six weeks. After a lapse of two years it recurred the third time, and it had remained stationary in size for six months and produced no discomfort except for its appearance. (Patient refused to submit to biopsy.)

GUMMA OF THE EYELID. Presented by DR. BEINHAUER for DR. WERTHEIMER.

A man, colored, aged 39, married, presented a lesion on the conjunctival surface of the left upper eyelid which began four months before as a small papule. During the last six weeks it had enlarged and ulcerated. The lesion was painless. The patient denied venereal infection, was married and had two children living and well; his wife had had one miscarriage at eight months. The conjunctival surface of the left upper eyelid presented an indurated mass the size of a pea with a centrally situated, sharply defined ulceration, the base of which was covered with a dirty gray purulent material. The surrounding tissue showed no secondary reaction. There was a unilateral submaxillary adenitis on the same side. The Wassermann reaction and repeated dark-field examinations were negative. Cultures showed *Staphylococcus aureus* and *albus*.

DISCUSSION

Dr. Guy said that he saw the case previously and that dark-field examinations, Wassermann and provocative Wassermann tests with mercury injections resulted negatively. He regarded the lesion as tertiary.

SYRINGOMA. Presented by Dr. Guy and Dr. Jacob.

A colored woman, aged 24, presented a deep seated papular eruption over the upper part of the chest. The individual lesions varied in size from 0.25 to 0.5 cm. in diameter. They were of firm consistency, hyperpigmented and shiny. Subjective sensations were lacking. The condition was of two years' duration. A section was presented which showed cystic epithelial masses and scattered epithelial strands in the corium. The epidermis showed slight acanthosis and an increase in the normal pigment.

DISCUSSION

Dr. Guy remarked that a few of the lesions fulgurated had disappeared entirely, and that the roentgen ray had had no effect.

Stanley Crawford, M.D., Secretary.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Regular Meeting, Oct. 9, 1922

Frank Crozer Knowles, M.D., *Presiding*

ICHTHYOSIS HYSTRIX. Presented by Dr. Corson for Dr. Knowles.

E. R., an unmarried white girl of 21, had no family history bearing on her case. She had always had a dry, harsh, somewhat crackled skin. Five years ago, it began to take on the characteristics now present. The face, scalp, palms and soles were normal, but the rest of the body was dry and slightly scaly throughout, with the exception of certain areas in which the disease took on more of a keratotic, almost verrucose appearance. These areas were noted chiefly on the flexor surfaces of the wrists and elbows, the axillae and ankles. On the points of the elbows there was no elevated thickening, but it was present over both patellae. The back of the neck showed marked lichenification with diamond-shaped figures. The dorsal surfaces of the hands and the extensor surfaces of the forearms also showed some lichenification, but had been improved by the use of roentgen rays.

Professor Lucien Pautrier of the University of Strasbourg, had seen the case a few days earlier and regarded it as one of erythrodermie ichthyosiforme congenitale.

DISCUSSION

Dr. Schamberg said that he regretted the last named definition, as he felt that the name of the basic condition was used as an adjective—an ichthyosis of an unusual type. He felt that the symptomatology placed it properly in this group. There was thyroid disturbance in some of the cases reported, though in others no such relationship could be traced.

DR. KNOWLES said that he agreed with the preceding speaker. No derangement of the thyroid had been noted in this patient.

CASE FOR DIAGNOSIS. Presented by DR. SCHAMBERG.

A mulatto girl, aged 19, presented an eruption of five years' duration. It consisted of pigmented patches, slightly raised and irregular, with a keratotic surface. It occurred on the back and sides of the neck, between the breasts and in the axillae. Subjective symptoms were wanting, and the condition was slowly progressing. In addition to the eruption described, pigmented macules were present over the chest, scrapings from which showed *Microsporon furfur*. Between the breasts were linear keratotic, pigmented elevations. Sections from a biopsy made by Dr. Greenbaum showed acanthosis, a considerable degree of keratosis and some slight inflammatory changes around the vessels and in the upper arm. There was considerable hypertrophy of the malpighian layer. The diagnosis of acanthosis nigricans was suggested. That condition was often associated with malignant disease of the viscera, but this patient seemed perfectly healthy otherwise. There was no disease of the mucous membranes. There was also the question as to the rarity of the disease in this race.

XANTHOMA TUBEROSUM. Presented by DR. GREENBAUM for DR. SCHAMBERG.

I. K., a Jewish tailor, aged 53, had noticed firm lumps on the left knee and right elbow for more than two years. On examination, a small group of hard nodules of reddish inflammatory color, some of them with orange tinted tops, four or five in each situation, were noted. The patient had presented himself for the first time, and detailed study had not been undertaken. No examination of the urine had been made. There was no discussion, as all considered the case to be one of xanthoma tuberosum, possibly of the diabetic type.

MACULAR ATROPHY. Presented by DRS. STRAUSS and SIDLICK.

A mulatto woman, aged 30, presented a more or less generalized eruption which had lasted for five years. In addition, two almost typical butterfly patches on either side of the nose had been present for two years and a half. It was thought that two conditions were present, an erythematosus lupus and a macular atrophy. She had received a great deal of treatment for the more widespread condition, directed toward the eradication of syphilis, which her former physicians had believed to be the condition present. The generalized eruption occurred chiefly on the trunk and arms and consisted of thickly set, puffy, foveated grayish-white scars, soft to the touch. There were no active lesions present on the trunk, but on the forearms and to a lesser extent on the upper arms were located a few reddish papules, each about the size of a small pea. They were almost uniform in size. The Wassermann test had been persistently negative.

DISCUSSION

DR. SCHAMBERG said that he found the case interesting on account of the great extent of the eruption. He felt that all would agree as to the diagnosis of the condition of the face. On the body were suggested the benign soft tumors of Schweninger and Buzzi. He recalled a case designated as atrophoderma pemphigoides shown before the Society two years before. He classed this disease as one of the atrophies.

Dr. Klauder expressed the opinion that this case was one of macular atrophy.

Dr. Schamberg said he did not agree, as the lesions were elevated; whereas those of macular atrophy were depressed, these were bulging. It would be interesting to have a roentgenogram of the chest. The association of these two conditions in one patient was unusual.

Dr. Weidman said he thought there was the appearance of former swellings with resultant atrophy.

ACRODERMATITIS CHRONICA ATROPHICANS. Presented by Dr. Weidman.

A white woman, aged 23, married, had a skin condition which began at the age of 4. A long linear tract of atrophic skin extended from the left shoulder down to the fingers of that hand. A small patch occurred on the index finger of the right hand. To the patient's knowledge there had never been any swelling or redness.

As far as the history went, the primary condition was an atrophy. No induration, pain or other objective or subjective symptoms had been associated. The patch was partly pigmented and in some portions depigmented. Roentgen-ray examination of the neck showed no cervical ribs or other swellings. The basal metabolism was normal.

DISCUSSION

Dr. Schamberg said that he regarded the case as one of linear morphea in the stage of atrophy.

Dr. Corson said that the case closely approached one of linear scleroderma he had seen but without any history of induration or interference with joint action at any time; this diagnosis seemed unlikely in this instance.

Dr. Crawford mentioned the possibility of some nervous disturbance being causative as the strip of eruption rather closely followed the course of the ulnar nerve.

Dr. Strauss said that there was a possibility of its being an atrophy following a herpes zoster.

KAPOSI'S SARCOMA. Presented by Dr. Weidman.

A white man, 66 years old, had been presented before the Society several years ago and was shown again, partly on account of the striking improvement. He had received a variety of treatment, largely roentgen ray and radium, at the hands of various practitioners. The disease consisted of purplish nodules on the lower part of the legs, the average size being that of a grape. Much atrophy from destruction of old lesions was also present.

DISCUSSION

Dr. Schamberg remarked on the great improvement which had taken place since the time when he presented the case. There was an appearance suggesting scleroderma and some warty and pigmentary changes, doubtless from radiation.

PARAPSORIASIS. Presented by DR. KLAUDER.

D. S., a white man, aged 24, a machinist, had been shown by Dr. Stelwagon in April, 1917. The condition had been present for nine years and appeared as slightly elevated, irregularly shaped, reddish patches, with a slight scale on the surface scattered over the body but located chiefly on the trunk. It was slightly itchy. The Wassermann test was negative. He had been treated with a chrysarobin preparation and radiation.

DISCUSSION

DR. SCHAMBERG said he felt that the case was one of erythrodermie pityriasique en plaques disseminées of Brocq. There was lichenification in some places. Others might call it parakeratosis variegata.

LUPUS ERYTHEMATOSUS. Presented by DR. KLAUDER.

An 18 year old colored girl had a reddish eruption with pigmented borders, extending almost completely around both eyes for a width of from 1 to 2 cm. There was the appearance of denudation of epidermis in the inflamed area. Smaller and disconnected patches surrounded the ears. There had been a gradual extension from a small beginning along each ear, the duration being two years. The Wassermann test was negative, and the case was clearly one of lupus erythematosus, but the presenter felt that the rarity of the condition in this race warranted its presentation.

EDWARD F. CORSON, M.D., Secretary.

MANHATTAN DERMATOLOGICAL SOCIETY

Regular Meeting, Oct. 11, 1922

H. J. F. WALHAUSER, M.D., *Presiding*

NEURODERMATITIS. Presented by DR. ROSEN.

A woman, aged 48 years, married, born in the United States, presented a rather extensive neurodermatitis. The parts involved were the bends of the elbows, neck, chest, lumbar region, flanks and popliteal spaces. This condition had been present about one year without any improvement from various local remedies.

DISCUSSION

DR. LEVIN agreed with the diagnosis of eczema and thought that it might be associated with an internal disorder. He cited a case he had recently observed, in which examinations revealed a carcinoma of the stomach.

SARCOID DARIER-ROUSSEY. Presented by DR. O. L. LEVIN.

J. B., a woman, aged 36, married, presented skin lesions of six years' duration. The lesions were present on the upper and lower extremities and the buttocks. They consisted of bean-sized to silver dollar-sized flat and slightly elevated bluish-red and purplish lesions. Although they appeared flat, it was found on palpation that they were deeply infiltrated and could be

lifted up like paraffinomas. Some of the lesions showed a slight apple jelly-like tinge. One lesion on the leg was ulcerated from applications of an irritating salve. A scar on the left arm, resulting from excision of the lesion, presented the same characteristics as the other lesions. Biopsy revealed tuberculosis. General examination disclosed no evidence of tuberculosis. The Wassermann tests were negative. On treatment with tuberculin there was marked improvement, and about 50 per cent. of the lesions had disappeared in about six weeks. Treatment with the roentgen ray had previously been of no value.

DISCUSSION

Dr. Levin said that the sarcoids of the Boeck and Darier-Roussey type showed under the microscope changes observed in other forms of tuberculosis, but rarely showed a tendency to necrosis or ulceration. He called attention to the fact that roentgen-ray therapy had been of no avail, while the results obtained with tuberculin were marvelous.

Dr. Oulman said that the tuberculosis bacilli in lupus were demonstrated by the antiformin method, and he asked whether Dr. Levin tried this method to find the bacilli in sarcoids. About a year ago, he presented a case in which injections of cacodylate of soda cleared the condition.

PAGETOID EPITHELIOMA. Presented by Dr. Bechet.

M. E., a woman, aged 52, said that the lesion had been present for three years. Six months previously a nodular ulceration had occurred in its center. Its growth had been very slow. On the right lumbar region was a lesion roughly rectangular in outline, about 1 inch wide and 1¾ inches long. It was pefrectly flat, sharply circumscribed, with a pinkish surface covered with small scales and crusts. In its center was a nodule undergoing slight central ulceration. The borders of the nodule were elevated and pearly in appearance. At the upper border of the lesion distinct atrophy was discernible. The nodule was typically epitheliomatous in appearance, and it was a question whether the patch was Bowen's precancerous dermatosis with an epithelioma in its center, or whether the whole lesion was a flat discoid epithelioma to which Darier affixed the name of pagetoid epithelioma because of its resemblance to Paget's disease.

DISCUSSION

Dr. Mount said that this lesion fits in with the so-called precancerous dermatosis of Bowen. The name is a poor one, because the condition is demonstrable epithelioma from the beginning. In the case under discussion there was a reddened scaly area circumscribed by a fine pearly border, which on close inspection looked as if it were made up of very small flattened papules. When this border was examined microscopically, it showed epithelioma. The scales when removed disclosed a moist red eroded surface. This condition is sometimes mistaken for sclerosed lichen planus, syphilis or eczema. The Bowen type of epithelioma is a much better name for the disease.

Dr. Rosen agreed with the diagnosis; he referred to the case of a woman 65 years of age who had an involvement of the breast, which began thirty years before, and which at the time of examination showed an extensive infiltration of the entire mammary structure. The patient was in good physical condition. This case is just mentioned to illustrate how slowly progressive Paget's disease may be.

HYDROCYSTOMA OF THE FACE. Presented by DR. WISE.

Mr. L. I., aged 56 years, had the disease for thirteen years. Scattered over the face were numerous pinhead-sized firm skin-colored somewhat translucent lesions about ⅛ inch in diameter. A biopsy was made but has not yet been reported.

DISCUSSION

All agreed with the diagnosis.

ANNULAR LICHEN PLANUS. Presented by DR. BECHET.

C. T., an Italian woman, aged 44, said that the eruption began fifteen years before. Most of the lesions were confined to the arms and legs, and consisted of shiny, violaceous umbilicated papules, irregularly quadrangular. A large number of them had coalesced to form perfect rings. The itching was, as usual, quite severe.

DISCUSSION

All agreed with the diagnosis.

ANGIOMAS OF THE TONGUE AND MUCOUS MEMBRANES OF THE MOUTH. Presented by DR. O. L. LEVIN.

A Russian, aged 39, married, said that the tumors first appeared ten years ago and were treated by Dr. Blaschko in Berlin with radium; following about twenty radium applications the tumors had disappeared. Six months before, the lesions began to appear again. As presented, the lower lip showed a pea-sized bluish-red soft tumor. The dorsum of the tongue showed a quarter dollar-sized depressed scarred area on which there was a bean-sized elevated globular purplish tumor. A similar small lesion was seen on the left border of the tongue, and the mucous membrane of the left cheek showed a nickel-sized scar area in which a new tumor was appearing. On the left cheek, just in front of the auricle there was an atrophic area with telangiectasia, a result of previous radium applications.

DISCUSSION

All agreed with the diagnosis.

URTICARIA PIGMENTOSA. Presented by DR. PAROUNAGIAN.

H. W., aged 51, a Roumanian merchant, had had a skin affection for twenty years. No venereal history was obtainable. The family history was good; the father died at the age of 70, the mother at 50, after an operation for hernia. Five brothers and two sisters were living and in good health, and none of them was afflicted with skin diseases.

The lesions consisted of macules, papules, wheals and pigmented remains of the older lesions. The entire body was involved. Itching was not a prominent symptom; he experienced slight itching only when he was over-heated. A number of Wassermann tests had been made, with negative results.

DISCUSSION

DR. LEVIN said that it was always difficult to make a diagnosis of urticaria pigmentosa, especially in the adult, and the question always arises whether the condition is not one of urticaria with pigmentation or urticaria pigmentosa. It is always important to have a diagnosis confirmed by a report on the pathology.

TUBERCULOSIS VERRUCOSA CUTIS. Presented by Dr. O. L. Levin.

T. G., aged 42, a technician of the department of pathology at Cornell, had a lesion over the metacarpal phalangeal joint of the index finger of the left hand. This lesion began six months before and slowly extended to its present size. As presented, the lesion was about 1¼ inches in diameter, elevated, sharply circumscribed, with a hard sloping border and a rough, scaly verrucose top.

DISCUSSION

All agreed with the diagnosis.

EPITHELIOMA. Presented by Dr. Wise.

The patient presented a lesion ¾ inch in diameter, which was clinically a basal cell epithelioma, but the duration was only five weeks. The rapid growth suggested the possibility of its being a prickle-cell cancer.

DISCUSSION

Dr. Bechet said that he had recently observed a large basal cell epithelioma, on the center of which a prickle-cell epithelioma had developed. On curetting the mass, it was found that the prickle-cell epithelioma had eroded deeply in the center of the basal cell. He would like to inquire as to the frequency of such an occurrence.

Dr. Oulman said that he had a patient over 70 years old with numerous sebaceous warts with carcinomatous degeneration, who developed metastatic glands which showed the basal as well as prickle-cell type.

Microscopic Examination: Prickle-cell epithelioma (Satenstein).

DERMATITIS VENENATA RESEMBLING LICHEN PLANUS. Presented by Dr. Wise.

M. S., an engineer, born in Austria, aged 34 years, had the disease for five weeks. The entire face presented a discrete papulovesicular eruption extending down to the neck. In places the papules were fused, forming patches of erythema. On the flexor aspects of the forearms, especially of the right, were papules and linear scratch marks. Similar but more pronounced lesions were present on the abdomen. The back of both hands showed circular crusted patches with slight oozing. On the thighs were many linear lesions. The inner side of the left leg showed a crusted erythematous patch.

DISCUSSION

Dr. Bechet thought that the lesions on the hands and arms resembled a dermatitis. The lesions on the legs strongly suggested lichen planus. The occurrence of the shiny papules in the linear scratch marks rather corroborated such a diagnosis. It was not, however, a typical eruption.

Dr. Levin said that the lesions present were those of a dermatitis (eczema). There were a few lesions present that suggested only lichen planus but were not the characteristic lesions of that disease.

Dr. Parounagian was of the opinion that the eruption was that of lichen planus, on account of the severe itching, symmetry, violaceous color and shining papules, in spite of the accompanying dermatitis, which might be due

to his occupation. He also suggested that Dr. Wise present the patient at the next meeting so that it might be observed whether there was any change in the condition.

DR. ROSEN agreed with the diagnosis of dermatitis from some external irritant. The patient also had an epidermophyton infection on the lower extremity. The diagnosis of lichen planus could be excluded if one carefully studied the character of the lesions, which were vesicopapular, although some were linear in distribution. He had the opportunity to study this case in daylight and failed to notice the presence of any lichen planus papules.

DR. GILMOUR said he believed this to be lichen planus, especially as there were characteristic lesions on the right forearm. He said that he thought the dermatitis was a secondary result of his occupation and scratching.

DR. OULMAN regarded the lesions on the arm, etc., as a secondary dermatitis in connection with the epidermophytosis of the leg. Microscopic examination: Dermatitis, subacute (Satenstein).

DUHRING'S DISEASE OR DERMATOPHYTOSIS? Presented by DR. WISE.

F. Q., a salesman, single, aged 46, born in Ireland, had the disease six months. The right axilla presented a sharply circumscribed pea-sized patch with an erythematous base and ruptured vesicles scattered throughout. There were similar lesions on the pubic region, extending backward to the perineum. There were a few papules around the umbilicus. The blood showed 1 per cent. eosinophils.

DISCUSSION

DR. LEVIN regarded the case presented as one of Duhring's disease. He called attention to several cases that he had seen recently, which may be divided into two classes: one, a mild form with few lesions, while the other, a severe form, showed widespread eruptions with pustule formation and marked reaction in the skin, which tended to go on to scarring and pigmentation.

ALOPECIA UNIVERSALIS. Presented by DR. LEVIN.

H. L., aged 29, a photographer, single, said that he had noticed a falling out of the hair of the scalp for about one and a half years prior to presentation. There was a gradual loss of hair of the scalp until there was complete baldness. This then spread to the hairs of the rest of the body, and within three months there was no hair on the body. As presented, the patient showed a total loss of hair in the usual sites. There was nothing in his past history to indicate an etiologic factor. He had had influenza three years before the onset of the condition. The Wassermann test was negative. The patient is to be thoroughly studied, especially in regard to metabolic disorders and disturbances of the internal secretions.

MULTIPLE PIGMENTED HEMORRHAGIC SARCOMA. Presented by DR. BECHET.

E. L., aged 67, a Polish Jew, who had lived in the United States for thirty-six years, said that he first noticed the eruption six months before. On the feet, ankles and around the knees, were large numbers of reddish-blue to purplish, pea-sized nodules, with here and there diffused infiltration of a verrucous

appearance. A considerable capillary dilation could be noticed around the nodules. An eczematoid eruption was also present on the legs.

DISCUSSION

DR. ROSEN had seen this case in the wards of the Mt. Sinai Hospital about three months before. At that time there was an epidermophyton infection present on the tumors, which gave the condition the appearance of a hypertrophic lichen planus.

REINFECTION IN SYPHILIS. Presented by DR. PAROUNAGIAN.

T. R., aged 42, a man, born in the United States, first reported at Bellevue, Aug. 10, 1921, presented remains of chancre in ano, and a generalized roseola of secondary syphilis. The Wassermann reaction was ++++. He said that he had been operated on for hemorrhoids six weeks previously, and that the eruption had been present about four weeks. The patient received a course of silver arsphenamin and after a total dosage of 1.95 gm., the Wassermann reaction became negative. The Wassermann reactions on Sept. 21, 1921, April 3, 1922, and Aug. 28, 1922, were all negative. On Sept. 18, 1922, the patient reported with a small ulcer at the coronary border, of three days' duration. He had been exposed five days and one month before. The dark-field examination was positive for *Spirocheta pallida* on Sept. 18, 19, Oct. 3 and 10, 1922. The Wassermann reaction was one plus on Sept. 19, 1922, one plus on Sept. 26, 1922, and two plus on Oct. 3, 1922. Another Wassermann test was made, Oct. 10, 1922. The lesions have progressed in size. A faint roseola is appearing.

DISCUSSION

DR. LEVIN said that a positive diagnosis of reinfection could not be made in this case, because all the data were not present. In order to make a diagnosis of reinfection, it was first necessary to prove that the patient had been cured of his first syphilitic infection. In this case, all the criteria of a cure were present except evidence of a negative spinal fluid previous to the onset of this apparently new infection. The most that we can say in a case of this kind is that it is a superinfection. If it can be shown that the spinal fluid was still negative, this may prove that the case presented was a reinfection.

DR. PAROUNAGIAN said that this patient was treated for his previous infection on our service, presenting anal chancre, roseola, condylomas and a four plus Wassermann reaction. On Aug. 28, 1922, his Wassermann reaction was negative. On Sept. 18, 1922, he reported with a chancre on the coronary border of the glans penis, with a history of exposure five days and a month before the appearance of his genital lesion. Dark-field examination on three occasions disclosed numerous *Spirochaetae pallidae*, each Wassermann test showed a stronger reaction, and the patient complained of headaches, sore throat and roseola, which should convince us that this was a case of reinfection.

EPITHELIOMA OF ALA NASI. Presented by DR. WISE.

H. F., a man, born in Austria, had a growth on the left ala nasi, seven years before. Six years before he received radium treatment. The left nostril

was almost entirely destroyed. Around the destroyed area the skin was bluish red and slightly edematous; it showed no definite nodules. Biopsy showed epithelioma, basal cell, and chronic radiodermatitis (Satenstein).

LUPOID SYCOSIS. Presented by Dr. Wise.

A. G., aged 44, born in Russia, married, an upholsterer, had a lesion for fifteen years. He had had practically no treatment. On the left side of the cheek there was a patch of atrophy and complete loss of hair measuring 2 by 4 inches. Along its margins, extending into the bearded region of the neck and hair line of the forehead the process seemed active, that is, there were isolated and confluent erythematous and pustular lesions involving the hair follicles. There was no improvement under roentgen-ray treatment.

D. L. Satenstein, M.D., Secretary.

CHICAGO DERMATOLOGICAL SOCIETY

Regular Meeting, Oct. 18, 1922

Harold N. Cole, M.D., *Presiding*

KERATOSIS PUNCTATA. Presented by Dr. Lieberthal.

A man, aged 44, presented an affection of the left palm, which had been present for over eight years. He did not know of any skin disease in his family, nor had he himself been subject to any except the present one. There were no subjective symptoms except a feeling of dryness. The palm was diffusely keratotic and showed pointlike depressions with horny plugs. The fingers in their proximal volar parts, in their webs and the dorsal extension of the latter, as well as the radial and ulnar sides of the left hand, were erythematous with a faint indication of keratosis.

Dr. Lieberthal said that when he first saw the patient he was not inclined to make a diagnosis of keratosis punctata, as the latter was described as a condition affecting both palms and soles without an erythema in the periphery.

DISCUSSION

Dr. Foerster called attention to the fact that Buschke and Fischer had described a condition clinically similar to this, and he thought a case was shown at the recent Minnesota meeting by Dr. Sweitzer. One of the striking features in this patient was that the disorder appeared on only one palm. He did not recall any similar limitation in other reported cases.

A CASE FOR DIAGNOSIS. Presented by Dr. Lieberthal.

A girl, aged 7, had lesions on the arm and back. The disease had been present for one and a half years in recurring attacks of blotches, which caused little itching but were gradually healing leaving white spots. Below the shoulder over the lateroposterior aspects of the humerus on each side there was a quarter-sized shallow, faintly pinkish nonsymmetrical plaque with roundish outlines, consisting of aggregations of minute flat papules closely set, with scanty desquamation. A similar lesion was present on the back

below the right shoulder, and on the medial side over the lower third of the right humerus there was a narrow, longitudinal, irregular papulocorneous streak. A long oval white spot was noted over the left cubita and a dime-sized one on the right arm, which were formerly the seat of plaques. The child was otherwise normal.

DISCUSSION

Dr. Senear said that he was inclined to think the condition was a seborrhoic process in a girl with keratosis pilaris. She had a number of comedones scattered over the scalp.

Dr. Ormsby said he thought it was an example of lichen spinulosis of Crocker. This disorder occurs in small patches in young children, about the neck, arms and trochanters, exactly where the lesions were in this case. As it clears up it may leave white areas, and he considered the case rather a typical one of that disorder.

Dr. Lieberthal said that he could not account for such an intensive pigmentary disturbance, considering that the original lesions were of such a mild inflammatory character.

A CASE FOR DIAGNOSIS. Presented by Dr. Stillians for Dr. Waterman.

An American woman, aged 24 years, a ticket agent, in May, 1921, had a febrile attack lasting four days, symptoms of a "bilious attack," with an eruption on the right cheek and upper central portion of the chest which lasted until October 1, then gradually faded under treatment. In April, 1922, she had another febrile attack which lasted for three days and was accompanied by sore throat, eruption on both cheeks, nose, ears and chest. The eruption had since spread to the chin, neck, hands, wrists and arms. There was no itching or pain. The Wassermann reaction was negative; the white blood count was 2,050 to 3,200 on four different occasions; the differential count was about normal. Careful search revealed no indications of chest involvement or any other internal disorder. Urinalysis revealed much indican, which cleared up, together with foul breath and perspiration, under treatment for colon stasis. There was moderate secondary anemia.

At the time of presentation, there was sharply defined erythema which involved the face, up to the lower lids, with the exception of a few areas under the mouth and nose. It was red and infiltrated with slight scaling. On the chest was a large, triangular, sharply infiltrated, ham colored patch with a deeper red line at the border, which was sharply raised. On the neck were several groups of large, flat papules. On the backs of the hands were slightly infiltrated papules and erythematous patches which did not cover the joints, over which the skin was clear. The right forearm was involved over the lower half of the extensor surface. There was a patch on the left upper arm and smaller ones on the right arm, the eyelids and forehead. Under the diascope a distinct yellowish infiltrate was visible.

DISCUSSION

Dr. Ormsby said that he saw the patient in May, 1922, when the trouble had been present for six weeks. At that time there was an eruption on the face and chest, and the lesions were very much as at present. There was swelling and considerable edema, with a bright erythema. The lesions were well defined. There was a slight scaling about the lips, and a few papules

about the neck. The patient gave a history of a similar attack, with increased temperature, in 1921. They considered it a recurrent toxic erythema from some internal infection, and he felt the same about it now as he did then.

Dr. Zeisler suggested the diagnosis of lupus erythematosus disseminatus, and he said that he thought the disorder should be differentiated from pellagra. The sharply demarcated triangular lesion on the upper part of the chest and the erythema of the face suggested this diagnosis. At the same time, a lesion on the upper arm, which was not exposed to sunlight and which showed some atrophy, indicated an acute disseminated lupus erythematosus.

Dr. Stokes said that he thought the case was one of lupus erythematosus and that the Society might be interested in hearing the results of three necropsies at the Mayo Clinic on similar cases. Each of these cases had shown mesenteric tuberculosis, although in one of them no tuberculous glands were recognized in the abdomen at exploratory operation. All of the patients had had lower abdominal symptoms which had led to diagnosis of typhoid, appendicitis, etc. During the past summer the Section on Dermatology had had a patient under observation, whose leukopenia reached 1,700 cells. The patient's temperature ranged between 102 and 104 F. for days at a time, with profound emaciation and a sudden myocardial collapse. A metastatic abscess appeared in the calf of the leg, which on drainage was found to contain streptococci. Repeated blood cultures were negative. Arthritic symptoms developed late in the course of the disease. The eruptive manifestations were those of a toxic erythema with a peculiar dry livid appearance of the skin of the face so often seen in disseminated erythematous lupus. A typical patch of discoid erythematous lupus had appeared on the cheek, and there were patches on the scalp which had been identified a year and a half before. The patient's temperature subsided by lysis, and repeated relapses occurred. There were mouth lesions so closely resembling tuberculosis of the mucous membrane that a consultant who had seen a good deal of mucous membrane tuberculosis requested that radium be used. It was remarkable what a proportion of these cases experience errors in diagnosis and presumably reach a fatal termination without identification.

During this boy's prolonged febrile attack, the eruptive manifestations gradually cleared up, only to reappear with each renewed outburst. Dr. Stokes said that he felt that disseminate erythematous lupus presents its peculiar clinical picture because of an etiology of which either tuberculosis or streptococcicosis is the basis, the exciting cause of the explosion being a combination of the infections. In all probability the tuberculosis furnishes the hypersensitive background and the streptococcal infection accidents produce the explosion.

Dr. Waterman asked Dr. Stokes whether his cases ever cleared up and then recurred.

This patient was employed by the elevated road and was referred to him by the surgeon for that company, who had been much interested in the case. At one time the eruption cleared up entirely, with the exception of a spot on the chest. The spots on the face, arms and fingers disappeared, so that the improvement was noticed by many people; but in forty-eight hours they were all back.

Four days before presentation, according to the statement of the patient's mother, the condition had cleared up again, but the following day the spots were all back.

There was a history of dementia praecox in the family, and the father was an alcoholic; but the patient presented no neurotic symptoms.

Dr. Waterman had exhausted every means to find the etiology. The tonsils had been removed; the sinuses examined; roentgenograms made of the gastrointestinal tract; the blood pressure was normal; the blood sugar normal, but creatinin increased; the urine was normal except for indican. When she was first seen, there was a very foul breath and a foul, musty odor from the body.

The skin was examined for the usual and unusual parasities. Cultures were made of the scales of exudate on at least one-half dozen kinds of culture mediums. The scales were examined for moles, yeast and the higher types of bacteria; the tropical parasites were also considered in the search, but all these gave a negative response. The patient had gained 15 pounds (6.8 kg.) in weight during the last two months.

DR. PUSEY said that he did not think the rapid appearance and disappearance precluded the view taken by Dr. Stokes. He had seen a patient with unmistakable lupus erythematosus on the face with toxic erythema lesions on the extremities.

A CASE FOR DIAGNOSIS. Presented by DR. STILLIANS.

A woman, aged 27 years, who presented small white spots on the back of the neck, shoulders and sides of chest, when she was 22 years old, had had deep red pimples on the back of the neck. They appeared in successive crops, not discharging pus, and gradually disappeared, leaving while papules. During the last year, she had noticed many new, small white spots on the back, shoulders and neck and the sides of the chest. These maculopapules varied in size up to 0.5 cm. in diameter. A hairdresser had given her some treatment with the electric needle.

DISCUSSION

DR. FOERSTER said he thought it was a case of acne keloid.

DR. STILLIANS agreed that it was the result of acne but said that he thought the development of the small hypertrophic lesions was interesting, some of them being a few millimeters in diameter.

RINGWORM OF NAILS FOLLOWING RINGWORM OF PALM. Presented by DRS. ORMSBY and MITCHELL.

A man, aged 38 years, presented a disorder of one and a half years' duration. In 1918, he had had an epidermophyton infection of the hands, feet and genitocrural region, which cleared up successfully under treatment; but there had been three recurrences.

At the time of presentation, the index and ring fingers of one hand and the middle and ring fingers of the other hand were involved. The involvement of the nails began about two and a half years after the first infection. The nail surfaces presented the usual wormeaten, crumpled appearance. The fungus had not been identified by culture, and it was not known whether or not the palmar eruption was due to the same organism as the nails.

DISCUSSION

DR. ORMSBY said they would treat the disorder with the roentgen ray.

LYMPHANGIOMA CIRCUMSCRIPTUM. Presented by DR. OLIVER.

A girl, aged 12 years, had had lesions since birth, which had grown with the child. On the right scapular region were groups of small, deep-seated vesicles, which resembled frog's spawn. There were no subjective symptoms.

DISCUSSION

Dr. Pusey said that he agreed with the diagnosis, and that he thought the case was exceedingly interesting.

A CASE FOR DIAGNOSIS. Presented by Dr. Hedge (by invitation).

A woman, 22 years of age, presented a lesion on the right palm, right thumb and thenar eminence which had been present for ten years. There had never been any lesions on the scalp, elbows, knees or elsewhere over the body. The lesion had been healed several times, but always recurred. The Wassermann reaction made on Oct. 14, 1922, was negative. The patient was in good health and had had no other dermatoses.

DISCUSSION

Dr. Oliver said that he saw the patient about eight years before, and that Dr. Ormsby saw her at about the same time. The lesion now was in about the same condition that it was then. They made a diagnosis of psoriasis then, and he thought there was no change. He asked what treatment had been used.

Dr. Hedge said that he had used the quartz light under pressure, and the condition had cleared up on three occasions. He believed it was psoriasis.

Dr. Pusey said that he believed a diagnosis of psoriasis could not be made on the basis of a lesion of the palm alone. In his opinion, the case was one of the dry type of dermatitis repens. The condition persists indefinitely. He had seen such a case in a farmer, which had lasted for twenty-five or thirty years.

Dr. Ormsby said that he did not recall having seen the case before, but his only impression at present was that it was dermatitis repens. He had had a case under observation for a long time. Sometimes there was a dry, scaling border, and sometimes this was vesicular.

Dr. Stillians said that he did not see the undermined border in this case, but with the great improvement under treatment it did not look like dermatitis repens to him.

Dr. Oliver said that when the patient was first seen there was much more undermining than at present. They had tried all the remedies suggested for dermatitis repens, and that diagnosis was considered but given up in favor of psoriasis, as it resembled that condition more then than at present.

A CASE FOR DIAGNOSIS. Presented by Dr. Senear.

A woman, aged 55 years, had fallen fourteen years ago and injured herself in the right supraorbital region. She opened the lesion with a needle and obtained pus. Later a swelling developed in the glabellar region. This was opened, but had not healed. Two other lesions had appeared on the forehead and been opened. At three of these openings, reddish tumors had appeared. The Wasserman reaction was negative, and there was no history or sign of tuberculosis in the case. The patient had received five injections of arsphenamin and some mercury a year and a half before.

DISCUSSION

Dr. Stokes said that he thought the amount of treatment this patient had received did not eliminate the diagnosis of syphilis. He spoke of a rare and

as yet unidentified tumor process invading the bones of the nose and palate, perhaps akin to gangosa or to "malignant granuloma" recently spoken of in the British literature, of which he had seen one case.

DR. COLE asked whether they had made a microscopic examination.

DR. SENEAR said that he had seen the patient only once before, in the surgical clinic, and there had been no opportunity for careful examination. The antisyphilitic treatment was given before they saw her.

CHONDRODERMATITIS NODULARIS HELICIS. Presented by DR. MITCHELL.

A man, aged 45 years, had had a lesion on the margin of the left ear for six months. It was exceedingly tender, making it impossible for the patient to sleep on the left side. At times there was, in addition, a considerable degree of pain. There had been at no time scale formation or erythema.

When first seen, July 19, 1922, there was a slightly elevated nodule, 1 cm. in length, along the margin of the upper pole of the ear. It was slightly yellowish and waxy in appearance. There was a crust approximately the size of a pinhead in the center. Under repeated applications of carbon dioxid snow and radiotherapy, there had been a marked decrease in the sensitiveness of the lesion.

DISCUSSION

DR. FOERSTER said he thought it was an instance of the condition described by him in 1917, and also by Winkler, as painful nodule occurring on the rim of the ear, which at times involves the cartilage. The nodules were always small, rose-red, less than wheat-grain-sized, firm lesions, described as very painful on pressure.

DR. OLIVER asked whether a number of these cases were not preceded by frost-bite.

DR. MITCHELL said that this type of case was first described by Winkler, whose article had been abstracted in the Year Book for 1915. The lesion was a nodule and not an epithelioma, and was preceded neither by keratosis nor by frost-bite. The lesion is extremely tender rather than painful, and does not yield to treatment. It was not a common disorder in his experience. He and Dr. Ormsby had had another patient with a similar lesion under observation for several years. This patient appeared in the clinic last summer. The patient presented worked indoors, and there was no question of frost-bite. The other ear was entirely free. Winkler gave the disorder the name of "chondrodermatitis nodularis helicis," carefully excluding keratosis and epithelioma. Dr. Mitchell said that before treatment the lesion was a nodule, slightly elevated, practically skin colored, with no erythema, and with a central crust the size of a pinhead. They saw keratoses in that location, probably half a dozen a day, but he had never seen a keratosis that in any way resembled this nodule.

DR. FOERSTER said that he had been interested in these cases for years, but had seen perhaps only ten or twelve. They were all identical, as much alike as two peas. He had never seen a hyperkeratotic patch as the first sign; there was no resemblance to hyperkeratosis, and the lesion was always a small nodule. There was no history of scaling, but the lesion appeared as a nodule at the very start. Several of these cases had shown a tiny central depressed area, like a pin-point, and sometimes the cartilage was involved in an inflammatory change.

DR. ORMSBY said that Dr. Foerster's report of this disorder came out just about the same time and entirely independent of any foreign report. The two reports were similar, and he thought Dr. Foerster entitled to just as much priority in the matter as Dr. Winkler.

A CASE FOR DIAGNOSIS. Presented by DR. STILLIANS.

A Jew, aged 55 years, had had Sternberg's tuberculosis over three years. This disease of the glands yielded to roentgenotherapy, but the patient had recently been losing weight. He was presented before the Chicago Dermatological Society in 1920 because of an indolent ulcer posterior to the anus, which healed under roentgenotherapy. About Oct. 5, 1922, the right ankle became swollen, and hemorrhagic areas appeared. The ankle was painful and tender.

At presentation, there were hemorrhagic areas on both ankles, with blood bullae averaging 1 cm. in diameter at the center of each area. Where the bullae had broken, ulcers with jagged borders, about 0.5 cm. in diameter and 0.3 cm. deep, were seen at the center.

DISCUSSION

DR. PUSEY said he thought that the lesions were those of dermatitis from stasis in the circulation of Thuley.

DR. STOCKS said he was impressed by the fact that the man had enlarged glands in the neck, and that some of his lesions were situated at points where trauma was not likely to occur. The lesions gave the impression of being a crop which had appeared almost at the same time, were bullous in character, and now presented dry necrotic centers that could be scraped out. He said he thought that the possibility of a tuberculid could not be dismissed, but that the extreme inflammatory reaction about the lesions was unusual.

DR. SENEAR said that the patient still had definite bullae on the leg, the contents becoming slightly purulent. He thought that a papulonecrotic tuberculid was the most probable diagnosis, but the other symptoms suggested that the whole process might be ecthyma.

DR. STILLIANS said that he saw the patient first with this eruption three or four days before. He believed that some of the lesions that were now broken down had been bullous. The case struck him as being some blood borne infection, and reminded him of some diphtheritic bullae he had seen. He wondered whether it could be a mixture of tuberculosis with some secondary infection—a very acute hemorrhagic tuberculid.

EROSIO INTERDIGITALIS BLASTOMYCETICA. Presented by DR. MITCHELL.

A Jewess, aged 40 years, had lesions which had been present for a year and a half in the first and third interspaces of the left hand and in the third interspace of the right hand. The left thumb was broken when she was a child, the break resulting in close apposition of the thumb to the hand.

The patient was presented because of the unusual location of the lesion in the first interspace, and to demonstrate the marked improvement resulting from the application of copper sulphate solution as a wet dressing.

DISCUSSION

DR. PUSEY expressed his appreciation at seeing these cases, and said he thought it was interesting to have them brought to the attention.

DR. COLE asked what strength solution was used and whether there was a continuous dressing of the copper sulphate.

DR. MITCHELL said that the patient was shown for two reasons: She had a broken thumb when a child, and as a result the thumb was in close apposition to the hand; and it was the first case in which he had seen the disorder in the first interspace. The patient had used Whitfield's ointment, chrysarobin and roentgenotherapy without benefit. It occurred to him that copper sulphate might be of value. He had tried it in two cases, applying it twice a day as compresses, and it had given better results than anything else he had tried. He had tried everything used in ringworm infection, and had used potassium permanganate in a half dozen cases over a long period of time, without any benefit.

A CASE FOR DIAGNOSIS. Presented by DR. STILLIANS.

A washwoman, aged 60 years, presented an eruption between the fingers which had been present for twelve years, never clearing up entirely. The lesions resembled those of erosio interdigitalis blastomycetica. No fungus could be found, but treatment with Whitfield's ointment caused marked improvement.

At presentation, fading lesions were present between the ring and little finger and between the ring and middle finger of the left hand.

Dr. Stillians said that at first they thought it was a case like those reported by Dr. Mitchell and that they would be safe in trying Whitfield's ointment. Since there had been an unexpected improvement with Whitfield's ointment, it was probably some other ringworm fungus. The lesions had been markedly erythematous with central erosions.

DISCUSSION

DR. PUSEY said he thought it was not the same condition as that in Dr. Mitchell's case.

DR. MITCHELL said he thought it was not of the same type. There was no collarette of scale, no whitened, sodden appearance, and the organism had not been found. Therefore, he believed the diagnosis of erosio interdigitalis blastomycetica was not justified at the present time.

URTICARIA PIGMENTOSA. Presented by DRS. ORMSBY and MITCHELL.

A Jew, aged 51 years, had had the disorder for two years. The lesions first appeared on the face during the summer. Later, they developed on the arms and trunk, and lastly on the hands. There had been only occasional mild itching. The lesions had not changed in appearance since the onset. Friction produced only moderate urtication. Microscopically, there was found no increase in mast cells.

DISCUSSION

DR. PUSEY said he considered it a case of acquired urticaria pigmentosa.

DR. MITCHELL said that that had been their diagnosis. There was only a moderate amount of urtication and a gradual onset. The lesions at first were

more violaceous than usual, but they had been unable to come to any other conclusion. The fact that mast cells were absent did not rule out this diagnosis.

LEPROSY (MIXED TYPE). Presented by DR. STILLIANS.

A Chinaman, aged 32 years, whose disorder was first noted three years ago, while working in the South Sea Islands, had at that time had an eruption of skin colored nodes scattered over the trunk and limbs, which disappeared spontaneously in about a month. The present eruption of nodules appeared on the right forearm accompanied with some sensation of numbness in the fingers, followed by ulceration which had resisted all treatment. Both ulnar nerves were palpable, with atrophy of the interossei of the right hand and loss of sensation in the tip of the right little finger. A filbert-sized epitroclear gland was palpable at the right elbow.

DISCUSSION

DR. OLIVER said he thought this man resembled very much the patient shown last winter who presented the maculo-anesthetic type of leprosy. He had had the disorder for eight years; it began on the legs and the patches on the body were much like the ones on this man's arms. The ulnar nerves were much thickened.

DR. LIEBERTHAL called attention to the feature of anesthesia and that the center of the patch was not a scar. He thought the patch was rather typical.

DR. STILLIANS said that he had seen the patient for the first time the day before presentation. Dr. Chan had tried to get a smear from the ulcers but was unsuccessful. There had been no attempt to get a smear from the nose. He thought the case was very suspicious of leprosy on account of the enlargement of the ulnar nerves, the anesthesia of the tip of the little finger and the atrophy of the interossei on that side. The patch had been treated with some irritating solution. The patient would be taken to the County Hospital where he hoped to be able to study the case further.

GRANULOMA INGUINALE. Presented by DR. EISENSTAEDT.

A negro, aged 38 years, had a penile lesion of seven years' duration. The Wassermann reaction was reported negative, but the patient had received antisyphilitic treatment several years before, consisting of twelve arsphenamin and approximately ninety mercury salicylate injections.

DISCUSSION

DR. STOKES asked whether antimony tartrate had been tried intravenously in this case. Dr. Harry Foerster had asked about the outcome of the case of the patient of whom Dr. Stokes spoke in January at the annual meeting. At that time several members of the Society had particularly advised the continuous bath. The outcome of an attempt to apply this treatment had been highly unsatisfactory. The final stage of two years' treatment, which had resulted in cure, was an excision by the actual cautery of the sole remaining lesion, carrying the excision down to the fascia of the gluteus maximus with a 3 inch (7.62 cm.) margin. This cautery excision healed until the ulcer reached the size of the original lesion, and then again came to a standstill. Whole thickness skin grafts reduced it still further in size. Finally, the following of a suggestion made by Dr. Irvine regarding the use of minute fractional doses of radium about the periphery, one minute exposures with a 20 mg. half strength plaque, had resulted in final healing.

DR. PUSEY said he thought these cases were essentially chronic ulcers in a peculiar area; the condition was sometimes leishmaniasis and sometimes a phagedenic chancroid. It was not always the same condition. He believed that in this negro there had been a chronic inflammation, which had caused a secondary elephantiasis which did not heal. He thought many of the cases were not typical inguinal ulcers, but chancroids. During the war he saw about 150 such cases in one group of negroes, the lesions varying in size from that of this one to those that covered the whole area. He said that he thought they were not all the same process.

DR. LIEBERTHAL asked whether Dr. Stokes' case was a chancroid.

DR. STOKES said that the case referred to had been an erosive and gangrenous balanitis in which a physician had attempted to inject oxygen subcutaneously. An enormous horseshoe-shaped ulcer involving all the external genitalia and extending posteriorly to the sacrum, had resulted. It had required four years to heal.

DR. LIEBERTHAL said he thought the point made by Dr. Pusey was very well taken. Most of these cases were not chancroidal. In those which were, the continuous bath would give relief.

DR. PUSEY said he had had one case in which the process was very similar to this, but it was a blastomycosis. The man had the unhealed areas following ulcers of blastomycosis.

DR. EISENSTAEDT said that he felt very much as Dr. Pusey did as to the clinical differential diagnosis between granuloma inguinale and phagedenic chancroid. Certain cases of the first type can be diagnosed by finding the Donovan bodies, but this is not a constant finding. He thought in a case of this kind that had not yet been worked up histologically it would be worth while to make an attempt with tartar emetic. He thought the possibility of epithelioma should be considered. He had had a case that was practically identical in which he had found epithelioma, and that case also was in a young colored man. He thought the case was interesting from this point of view.

A CASE FOR DIAGNOSIS. Presented by DR. STILLIANS.

A man, aged 34 years, who had been well until three weeks previously, two weeks before had developed some pimples on the leg, which looked like boils. He had had a genital lesion ten years before. The Wassermann reaction was three plus. About some bullet wounds which were received in 1917 were follicular papules with a corymbose arrangement.

DISCUSSION

DR. PUSEY said that he considered this a corymbose syphilid—a large nodular lesion with small papillary lesions around it. He did not think it was due to a syphilis ten years before, but that the man had forgotten that he had had a chancre, probably ten or twelve months before.

DR. STILLIANS said they had considered the lesion a syphilid but had never seen a corymbose syphilid with such horny folliculo-papular lesions.

DR. STOKES asked whether any of the gentlemen present had been impressed with the frequency of the corymbose syphilid as a form of recurrence in inadequately treated cases.

DR. ORMSBY said he thought former experience with syphilis would answer that question. Most of the corymbose syphilids occurred from the ninth to the twelfth month after infection with or without treatment, as used before the discovery of arsphenamin.

DR. STILLIANS said that he once saw corymbose lesions occur during treatment with vanadium. This was the case that discouraged further research with this drug.

DR. MITCHELL said that he had seen this occurrence as a result of inadequate arsphenamin therapy in the clinic quite frequently.

LICHEN PLANUS HYPERTROPHICUS. Presented by DR. STILLIANS.

A negro, aged 40 years, had had the disorder for seven years. There were lesions on the right leg and on both forearms, dark brown, slightly raised horny patches.

DISCUSSION

DR. PUSEY said he thought it was valuable to bring in these cases. He liked to see a lichen planus in the negro, and he considered the case very interesting.

Book Reviews

X-RAY DOSAGE IN TREATMENT AND RADIOGRAPHY. By WILLIAM D. WITHERBEE, M.D., Radiotherapist, Presbyterian Hospital, New York, and JOHN REMER, M.D., Radiotherapist, New York Hospital. Cloth. Price, $1.75. Pp. 87, with 3 illustrations. New York: The Macmillan Company, 1922.

Witherbee and Remer's book is devoted to a statement of the method of roentgen-ray measurements which has been popularized in dermatology, especially by MacKee. It gives in detail the facts which it is necessary to know in order to apply the method, and it is a useful book. The description of the details of the method is, however, involved and difficult to follow, and in future editions it is to be hoped that the authors will make their statements simpler.

THE VENEREAL CLINIC. The Diagnosis, Treatment and Prevention of Syphilis and Gonorrhea. A Handbook of Venereal Disease in Relation to the Individual and the Community. Edited by ERNEST R. T. CLARKSON, M.A. (CANTAB.), M.R.C.S., L.R.C.P.

SYPHILIS OF THE INNOCENT. A Study of the Social Effects of Syphilis on the Family and the Community. By HARRY C. SOLOMON, B.S., M.D., and MAIDA HERMAN SOLOMON, A.B., B.S.

These two books differ from the ordinary works on syphilis and venereal diseases, chiefly because they place emphasis on the social aspects of these diseases. Both are to be commended, especially for this feature.

"The Venereal Clinic" gives an adequate presentation of the diagnosis and treatment of venereal diseases.

It would seem to the reviewer that "Syphilis of the Innocent" is not a good title for the second book; a much better title is the subtitle, "A Study of the Social Effects of Syphilis on the Family and the Community." This is a well done study, made under a grant from the United States Interdepartmental Social Hygiene Board, and it takes up the many aspects of the social problem of syphilis. It is free from the "sob stuff" that mars so much of this sort of literature, and is a commendable book.

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